COMPUTATIONAL MODELING OF SPONTANEOUS BEHAVIOR CHANGES AND INFECTIOUS DISEASE SPREAD

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COMPUTATIONAL MODELING OF SPONTANEOUS BEHAVIOR CHANGES AND INFECTIOUS DISEASE SPREAD

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SUMMARY

In the Spring of 2009, a new strain of pandemic influenza virus emerged in the human population and spread to major countries worldwide. This caused panic that the world was witnessing another influenza outbreak potentially of the size of the 1918 Spanish Influenza outbreak where a fifth of the world's population was affected. Although, this fear did not come to pass, the threat of a potentially deadly outbreak remains. The ability to mitigate and contain a disease is a vital aspect of any country's response strategies. Through modeling and simulation of the spread of an outbreak, decision-makers can better plan mitigation and containment strategies. This dissertation investigates how changes in human behavior affect the spread of pandemic influenza in the U.S. population using an agent-based computational model. The dissertation argues that more aspects of human behavior such as people's attitudes and trust in government-issued health advisory information about the disease need to be integrated into population-level models of pandemic influenza to improve model realism. I present a framework for incorporating such factors into computational models of disease spread to simulate possible scenarios that the spread may take to improve policy insights. I created models to represent different configurations of the attitudinal disposition of the population and then examined how agents representing individuals responded to the interventions implemented. The study revealed that a population that responds positively to government interventions reduced overall disease impact in comparison to the other scenarios modeled. Although the model is built on the U.S. population, it may be generalized for other synthetic populations in the future.

CHAPTER I

INTRODUCTION

1.1 Motivation

Over the last decade or two global attention has been increasingly drawn to the potential impact that fast-spreading, cross-border, severe infectious diseases can have on socioeconomic stability, political life, and the national security of states [95, 223, 70, 84, 96]. In the past, concerns about the impact of these communicable diseases in the population focused on those that are slow-spreading and predictable, thus more suitable for population studies. Examples of such diseases include the human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), sexually transmitted diseases (STDs), polio, and malaria. Fast spreading respiratory diseases such as severe acute respiratory syndrome (SARS), pandemic influenza, and even highly virulent and increasingly drug resistant pathogens (like *Staphylococcus aureus*) are getting renewed attention because they now pose more of a global threat than previously acknowledged [166, 72].

While disease-causing microbes have threatened human health for centuries, they have often been limited by the lack of an efficient transmission mechanism. However, the combination of the rapid growth of the human population resulting in activities that expose us more to deadly diseases—new and old, and our increased mobility which can aid their proliferation, provides new fuel to age-long fears that fast-spreading severe infectious diseases can potentially cause us large-scale societal disruptions, or even in the extreme case, extinction of our species [281, 259, 221]. Regardless, these diseases pose to us a near and present danger and our ability to be better prepared to recognize and rapidly respond to their spread in the population is important to decision-makers such as politicians, policymakers, and health practitioners who seek to contain them.

Pandemic influenza is one of those fast-spreading diseases feared by decision-makers because the pathogen is unpredictable, reoccurring, and can sometimes be virulent in the

human population. The seasonal influenza outbreaks which we typically experience every year is estimated to result in 25 – 50 million cases in the United States alone[1], and between 30,000 – 40,000 deaths annually [248]. Yet this is viewed as mild in comparison to the potential harm that the virus can cause. The best modern example we have of the damage that pandemic influenza can cause is the 1918 – 1919 *Spanish Influenza* outbreak which affected about one-fifth of the world's population and killed an estimated 50 million people[2] worldwide in about 18 months [293]. It affected about one-quarter of the U.S. population (about 25 million people then [44]) of which about 675,000 (3%) died [104]. In comparison, *'the great war,'* World War I, claimed just about 16 million lives, while *'the good war,'* World War II, *the war to end all wars* and the deadliest military conflict in history, claimed about 50 – 80 million lives [291]. When virulent, pandemic influenza viruses have the potential to cause staggering and mortality cases of unimaginable proportions in the human population.

Because of the unpredictable nature of the virus, there is a high degree of uncertainty in selecting response strategies to adequately mitigate and contain the outbreak of the disease [114, 246]. In addition, the ability to generalize mitigation and containment strategies from the risk factors of seasonal influenza to the pandemic version is also unclear. As a result of these uncertainties, the science behind preparing and responding to pandemic influenza can sometimes be vague, making the implementation of policy difficult [247]. Nevertheless, policymakers, health practitioners, and other stakeholders interested in mitigating and containing the disease need tools that can help them prepare and respond to an outbreak, even if the science behind them are limited.

For decision-makers, a top question in their minds is: "How would a modern-day influenza pandemic affect the U.S. economy?" Putting a value on the impact helps in determining how to prioritize the problem and thus determine the importance of the preparedness and containment tools. In this case, the Congressional Budget Office (CBO) estimated that

[1]The World Health Organization (WHO) estimates the average global burden of seasonal influenza to be as high as 1 billion cases and 3 – 5 million cases of severe illness [1].

[2]Why the Spanish Flu had such a high death toll is a subject of debate beyond the scope of this thesis. Interested readers may consult [266, 232, 205, 224] for more discussion on some of the possible reasons.

a pandemic on the scale of the 1918 outbreak could result in a loss of 5% of gross domestic product (GDP), or a loss of national income of about $600 billion [213]. The need to better underpin pandemic influenza policy decisions by improved disease spread models is an imperative because those decisions can have significant economic repercussions, even if their implications for other aspects of the basic functioning of society and national security are not included [95, 223, 70, 84, 96].

Modeling and simulation offers these decision makers a suite of tools that can be used to examine complex phenomena like the spread of infectious diseases and provide insights into some of the dynamics involved when social interactions and population variation are important factors. In particular, *computational modeling*[3] (in comparison to traditional mathematical models) offers the capability to capture more about the phenomena of interest in the model in a rigorous way thereby greatly increasing the level of realism that can be incorporated without sacrificing analytic focus [265].

In this dissertation, I investigate how changes in human behavior affect the spread of pandemic influenza in the U.S. population using a computational model. The result of this work is a model that can be used by decision makers to make projections of the progression of a pandemic outbreak and its implications at the population level so that better preparedness and response programs can be crafted. Policy modelers who tackle complex problems like pandemic influenza need improved models like this to better underpin policy decisions. Specifically, I used an agent-based modeling approach (a part of the computational modeling toolkit) to create a framework for simulating possible scenarios that a spread of the disease may take to improve policy insights. Because agent-based models (ABMs) are *generative*[4], they offer the additional advantage of an ability to uncover potentially unanticipated system responses that an intervention or policy may trigger [86].

[3] A computational model broadly defined is a mathematical model used to study the behavior of complex systems. Typically, it requires extensive computational resources. Examples of common computational models include weather forecasting models, turbulent flow models, molecular protein folding models, and earth simulator models. Some of the methods used to create the models in this domain include agent-based models, artificial neural networks, and membrane computing [265].

[4] The term 'generative' is typically used in this context to mean the ability of an agent (in an ABM) to sometimes display new complex behavior given simple behavior rules as input [86]. They are more commonly referred to as 'emergent' behaviors.

Importantly, ABMs are particularly useful tools for approximating real-world experiments to inform policy choices for when setting up field experiments for the phenomena might be expensive, unethical, time-consuming, or even outright impractical.

Although this study is focused on the U.S. population, the results obtained may be applicable to other populations with similar attributes. However, it should be noted that because computational models are more explanatory than predictive[5], more effort would be needed to re-parameterize the model developed here to suit other populations of study.

It is important to recognize that no model is perfect. While they can be used to forecast, the results must be received with some caution as it is the model data and underlying assumptions shaping the model algorithms that really determine the kind of results to be obtained.

1.2 Pandemic Influenza & Human Behavior

Although modeling the impact of human behavior on the spread of infectious diseases such as pandemic influenza is a discipline with a rich history steeped in traditional mathematical modeling [153, 17, 10, 69, 109], progress in this discipline also requires integrating a wide range of inputs from the behavioral sciences [108, 109]. The real challenge[6] in this domain centers on how to model the interplay between human behavior and the spread of infectious diseases [87, 184]. Because both human behavior and the mechanisms of disease emergence and spread in a human population are both complex processes, representing them in models is challenging.

For pandemic influenza, the behaviors of interest are those preventive actions that can affect the transmission of the disease, in this case, at the population level. These actions are a combination of pharmaceutical (vaccination and antiviral drugs) and non-pharmaceutical (all forms of social distancing) measures [100, 101, 181, 114, 179, 125]. Although it is still

[5]Prediction focuses on the output of a theoretical model while explanation focuses on the model itself [265, p. 5]. Computational modeling largely focuses on the model itself in an effort to increase model complexity by adding more real-world attributes to increase the explanatory power of the model (i.e., increase the descriptive realism of the models).

[6]This challenge has given rise to a new discipline called *Behavioral Epidemiology* – a new branch of epidemiology focused on the complex interplay between the determinants of human behavior (for example, risk perception and information) and the transmission and control of infectious diseases [184]. It integrates a wide range of tools and insights from the behavioral and traditional sciences.

unclear how and why people choose these behaviors (or comply with the health advisory information issued by authorities to protect themselves), the general assumption is that most people would like to take preventive measures against the disease. However because different people have different opinions toward what constitutes their safety, they may take different (and some times, contradictory) courses of action yet have the same goal in mind. For instance, while one individual may have a favorable attitude towards accepting a pandemic vaccine, the other may have an unfavorable attitude and thus reject it. Further, another individual may have an indifferent attitude towards the vaccine and so arbitrarily decide to accept or reject it [252, 139, 253, 288]. In addition, both behavior and disease also influence each such that it can sometimes be difficult to tease out the direction of causality between the two.

Incorporating these heterogenity in behaviors (across individuals, contexts, or time) and variations in causality into modeling frameworks can be quite challenging because of the computational complexities involved. Yet these *behavior-disease* models are vital for improved model realism because they have policy implications for mitigating the disease [179, 126, 302, 99, 211, 100, 222, 175, 181, 109]. Unlike traditional mathematical models, computational models that are spatially explicit[7] are best for modeling disease spread phenomena because the features of interest can be explicitly incorporated into the model and the effects studied.

Although several models have been proposed to study human behavioral responses and epidemic spread [89, 87, 160, 108, 109, 222, 139], and some have been applied to pandemic influenza outbreaks with interesting results [226, 99, 100, 101], current large-scale population models lack these psychological features that can help improve model realism [92, 219, 5, 218, 125, 64, 191, 98, 107]. These features such as perception and attitude towards disease risk, play important roles in the spread of the disease as observed during the most recent outbreak—the 2009 H1N1 pandemic influenza outbreak [262, 250, 270].

[7]The term "spatially explicit" is used in the sense of spatially explicit population models typically used in ecological studies. These are models that combine a population simulator with a landscape map for studying various effects on a population, for example, the effect of changing landscape features on population dynamics [202]. This has given rise to "spatial epidemiology" where spatial variations in disease risk or incidence are studied [216, 81, 233, 234].

In this study, I introduce three psychological features—*information* (i.e., the ability for agents to be informed about a disease in the course of an outbreak), *attitude* (i.e., an agent's inclination towards manifesting a behavior), and *resolution* (i.e., the decided course of action) into a large-scale, multi-agent system for simulating the spread of pandemic influenza. Because the behaviors are in response to a situation (shaping the perceived risk of infection), I modeled them as happening *"spontaneously"* as is typical in these kinds of studies [226, 99, 100, 101]. This means that they are conceived as happening quickly. For example, when an agent in the system is presented with the option to vaccinate, the agent decides immediately to accept, reject or be indifferent to it. This spontaneity assumption enables us to bridge the *intention-behavior* gap[8] by removing the time delay between intention, in this case framed as the time between being informed about a disease and the recommended protective actions to take, and the final action actually taken. Disease spread is then simulated through modeling the interaction of the agents with each other, which drives disease transmission.

The research questions raised by the above discussion are thus:

1. How do humans behave in general during a severe pandemic influenza outbreak?

2. How can human protective behaviors be represented in population models for simulating the spread of pandemic influenza?

3. How can some of the heterogeneities in human behaviors be incorporated into a computational model for simulating pandemic influenza spread in a population?

4. What are the policy implications of using such models as a basis for preparedness and containment plans for the disease?

[8]The intention-behavior gap phenomenon is the discrepancy noticed between intentions and ultimate behavior [102, 7, 8, 261, 255]. Expressed simply, an individual may develop an intention to change his or her health behavior, but may end up not taking the action or fully carrying it out to its logical conclusion (i.e., a form of the patience adherence problem [28, 91, 276]). How big the gap is remains unclear as several complex psychological variables govern it.

1.3 Dissertation Goal & Methodology

The main goal of this dissertation is to investigate how some of the preventive behaviors humans exhibit during an outbreak of pandemic influenza in a population can be incorporated into computational models suitable for simulating pandemic influenza spread. This goal is geared towards the development of a modeling framework that key decision makers can use to examine policy intervention strategies for containing the spread of the disease. The goal also aligns with the desire of the WHO Global Influenza Program (GIP) to provide member states with strategic guidance and technical support to help member states better prepare and deal with the threats of the disease [294].

The following objectives underpin the goal:

1. To research and document the behaviors people exhibit in response to the outbreak of pandemic influenza in a population;

2. To develop a computational modeling framework that can model some aspects of these spontaneous behaviors for simulation and analysis;

3. To examine some of the policy implications provided by the use of the model to investigate alternative interventions.

To achieve the first objective, I conducted a comprehensive literature review of studies that examined human responses to pandemic influenza, especially in the context of the most recent outbreak which occurred in 2009. Although modeling the influence of human behavior on infectious diseases has been a recent concern [108, 109, 107], adequately incorporating the insights from these studies into modeling efforts is still quite challenging as noted by the authors. My efforts at bringing psychological perspectives of human behavior into disease modeling has resulted in a framework where such factors are recognized and developed into a computational model.

To achieve the second objective, I developed a computational modeling framework based on the *Global Scale Agent-based Model* (GSAM) developed by Parker and Epstein [219]. This multi-agent system allows us to represent each individual in the population as a virtual agent

and equip them with the attributes of the behaviors desired.

Finally, using the model developed, I performed several scenario analyses to see how varying disease parameters and behavior interventions impact the spread of the disease.

1.4 Contributions

The primary contributions of this dissertation as follows:

- *A computational model framework that is capable of simulating spontaneous human behavioral responses for pandemic influenza spread analysis.* I developed a computational model framework, *Multi-Agent Simulation System for Analyzing Pandemic Influenza Spread* (MASSAPIS), which is capable of modeling spontaneous human behavioral responses that take place in the context of an outbreak of pandemic influenza. The framework extends the GSAM model by endowing agents in the model with spontaneous behavioral response capabilities such that agents can respond to the threat of infection in different ways and thus impact the spread of the disease in a diverse manner.

  Agents in the model are 'endogenized' with three psychological features or constructs—attitude, trust, and resolution to enable them to decide on how to choose preventive behaviors in response to the outbreak.

- *Added additional behavior capabilities to improve model versatility* I improved the versatility of the model for behavior-disease modeling by implementing three additional protective new features—vaccination, social distancing, and school closure in the model to improve the versatility framework.

- *An enhanced graphical user interface for configuring the model for scenario analysis to inform policy.* I extended the user interface with several menu options that added more functionality to the model and also created a dashboard for displaying the simulation results as the simulation progresses.

1.5 Dissertation Overview

This dissertation is organized as follows:

Chapter 2 documents research on artificial societies and emergent systems, human behavior and disease spread relevant to the dissertation. Studies in health behavior models, human behavior, disease spread dynamics, psychological factors affecting pandemic influenza and current models of disease spread are also discussed and reviewed.

Chapter 3 describes the theoretical background and some frameworks to facilitate understanding of modeling human behavior and infectious disease systems. It draws from the researches in the behavioral and traditional sciences as well as the recent 2009 outbreak to lay the foundation for incorporating the psychological variables into the framework.

Chapter 4 describes the computational model—Multi-Agent Simulation System for Analyzing Pandemic Influenza Spread, a framework capable of simulating spontaneous human behavioral responses to the threats of infection during a pandemic influenza outbreak. The structure of the framework, computational methods, and essential procedures needed for the operation of the model are described here.

Chapter 5 presents the simulation results, validation, and discussion. The simulation results consists of plots of disease incidence and burden for different scenarios of disease severity—ranging from a low-level to a high-level of infectiousness. The validation method is described, underlying assumptions are stated, and the discussion on the results are presented.

Chapter 6 summarizes the contributions of the dissertation and suggests potential areas for future research.

CHAPTER II

BACKGROUND

2.1 Overview

In this section, I present some useful background information about influenza and epidemic modeling to contextualize my study. First, I present an introduction of the history of influenza and discuss its emergence in the human population. Then, I summarize its virology, biology, and taxonomy to familiarize the reader with the key issues that surround the transmissibility of the disease as well as the mitigation and containment strategies commonly employed. Second, I also present some background information pertinent to modeling the spread of infectious diseases in the human population. Here, I briefly discuss the historical emergence of epidemic modeling and spotlight the groundbreaking classical *susceptible-infected-recovered* (SIR) model that revolutionized modern epidemic modeling and is the foundation of the disease model used in this study. Finally, I briefly discuss the types of epidemic models and introduce computational, agent-based, epidemic modeling to the reader.

2.2 Influenza

It appears that influenza, or *'the flu,'* as it is commonly known, may have been around for thousands of years, with six thousand years a reasonable estimate. Since the earliest descriptions of influenza-like disease by *Hippocrates*, the 'Father of Western Medicine' in 412 BC [20], and the numerous outbreaks reported in the middle ages[1], to the first recorded account of the pandemic in modern history in Russia in 1580 [227], to the 1918 pandemic which infected nearly a quarter of the world's population and resulted in deaths estimated close to 100 million people [266, 232, 224], influenza has lefts its mark clearly on human history as an old enemy emerging with new threats and as one of the most feared killer

[1]For example, an Irish manuscript in the fourteenth century mentioned an epidemic in Ireland with symptoms similar to influenza (and seen in the British Islands in 1510 [268, p. 1])

diseases of our time that cannot be cured but only contained.

The influenza virus can exist[2] in an endemic, epidemic, or pandemic state in a population [158, 159]. For clarity, an endemic disease refers to diseases that are present in the population and remain so at a low-level of potentiation (i.e., affecting only a small number of people) for a long period of time. An epidemic on the other hand affects a significantly larger number of people in a region or country at the same time (usually for a short time period of time) before the disease is contained and stopped. A pandemic, however, is an epidemic that spreads beyond the region or country where the disease emerged, and often with high morbidity and mortality rates. The seasonal influenza that we see yearly comes in either endemic or epidemic forms [227], but the major outbreaks that are pandemic in nature are the focus of this dissertation.

Influenza's viral mechanism constantly changes to perpetuate the disease, hence, its apt description as an *"unvarying disease caused by a varying virus"* [158]. Its varying features include generation by different genetic mechanisms originating from animal populations or human populations or from a mix of both populations[3] [284]. The pandemic-prone virus is often novel, occurring irregularly (typically, every 10 - 50 years in recorded history [292, 293, 159]), in multiple outbreaks or "waves" [179, 266, 200, 131], and varying greatly in severity [140, 176]. These traits also result in variation in the level of responses taken to address the disease [100, 101, 181, 114]. Information on the four major influenza pandemics of the last one hundred layers is summarized in Table 1.

The most recent pandemic, the influenza A/H1N1 outbreak of 2009-2010 (also known as the *Swine Flu*[4] outbreak of 2009), gave the world its first major pandemic in about 41 years. The virus, first recognized in 1919, arose as a result of a series of genetic shuffling events (viral re-assortments often through co-infection) between avian, swine, and human influenza

[2]Influenza viruses exist in both human and animal populations and remain in circulation in both populations for a long time period [158]. Its spread in the human population is the focus of this study, and its role in animal reservoirs is not considered here.

[3]Webster et al.'s hypothesis is that aquatic birds are the primordial source of all influenza viruses and that pigs probably serve as intermediate hosts in the genetic exchange. Geographically, they suggest that most new pandemic influenza viruses originate from southern China making the Southeast Asia region the 'cradle' which may originate the next virus [284].

[4]Sometimes it is referred to in literature as *swine-origin influenza virus*—S-OIV [112, 115] or pandemic H1N1 (pH1N1) virus.

Table 1: Characteristics of the four major pandemics of the last century.

Pandemic	Area of Emergence	Influenza A Virus Subtype	Estimated Reproduction Number	Estimated Case Fatality Rate	Estimated Attributable Excess Mortality Worldwide	Age Groups Most Affected	GDP Loss
1918 − 1919 "Spanish Flu"	Unclear	H1N1	1.5 − 1.8	2 − 3%	20 − 50 million	Young adults	−16.9 to 2.4
1957 − 1958 "Asian Flu"	Southern China	H2N2	1.5	< 0.2%	1 − 4 million	Children	−3.5 to 0.4
1968 − 1969 "Hong Kong Flu"	Southern China	H3N2	1.3 − 1.6	< 0.2%	1 − 4 million	All age groups	−0.4 to (−1.5)
2009 − 2010 "Swine Flu"	Mexico	H1N1	1.3 − 1.7	< 0.02%	284000	Children and young adults	Unknown

Source: The first three rows of this Table was obtained from [293, p. 13]; the last row data (Swine Flu) was obtained from the following sources—area of emergence [271], ii) estimated reproductive number [303], estimated case fatality rate [152], estimated attributable excess mortality worldwide [72], and age groups most affected [62].

viruses in circulation to produce the 2009 A/H1N1 virus strain in a swine reservoir. This became the first virus of pandemic potential that did not emerge with a distinct subtype[5] but rather a variant of the 1918 virus. It was also the first in recent history to emerge from North America [115], and not the region of Southeast Asia/China where most have come from [284].

It is not known when the next pandemic will strike, however, experts believe that the world is due for another one soon. In fact, the history of pandemics reminds us that each passing year of non-incidence brings us closer to the coming outbreak. As the world gets increasingly more interconnected, interdependent, and highly mobile, infectious diseases such as pandemic influenza will pose an even greater risk to modern civilization than ever before [156].

2.2.1 Virology, Biology, and Taxonomy

Influenza is a highly contagious respiratory tract infection caused by influenza viruses of the Orthomyxoviridae family that can infect both humans and animals [68, 105]. Three

[5]See Section 2.2.1 for an explanation of this term.

antigenetically distinct types of the viruses are known to exist—types[6] A, B, and C. Types A and B are common causes of the acute respiratory illnesses associated with the name of the disease. However, it is the type A viruses that have the genetic potential to become pandemic, and are thus the focus of this study. This is because type A viruses have the capacity to change forms and be transmitted from animals to man—a requirement for an outbreak in the human population. Type B viruses cause most of the seasonal epidemics while the type C viruses are believed to cause mild infections, endemics, and in some cases, cause infections with no symptoms at all.

The type A viruses are further categorized into *subtypes* according to the antigenic and genetic nature of two main proteins found on the surface of the virus cell. These *glycoproteins* are known as *hemagglutinin* (abbreviated in literature as H or HA) and *neuraminidase* (abbreviated as N or NA) proteins. Hemagglutinin agglutinates (i.e., clumps) human red blood cells and catalyzes a cell's absorbing the virus while neuraminidase cleaves sialic acid from the cell surface and progeny virions[7] to catalyze the release of the virus from infected cells[8]. For classification, the proteins are designated by numeric numbers that identifies the strain. For example, the "H5N1" virus designates an influenza A subtype that has 5 hemagglutinin and 1 neuraminidase proteins. Currently, up to 18 H and 11 N proteins have been identified [269]. In reality, many different combinations of H and N proteins are possible, hence creating potentially many different subtypes. Most circulate in the avian population [9], and in some mammals—for example, horses (H7N7 and H3N8) and even in dogs (H3N8) [54]. In the human population, viruses with four different H subtypes (H1, H2, H3, and H5) and two different N subtypes (N1 or N2) have been identified [217, 73], however, health authorities believe two chief subtypes—H1N1 and H3N2 are currently in general circulation as at today [54]. Figure 1 shows a summary view of the major human influenza virus subtypes in modern history and the relative dates of their introduction into circulation. Influenza B viruses are not known to exist in different subtypes [68].

[6]Type A was first isolated in 1933 [260], type B in 1940 [106], and type C in 1947 [267].

[7]A virion is the complete infective form of a virus outside of a host cell. It consists of an outer protein shell called a capsid and nucleic acid core–either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

[8]Interested readers may check the following references for a more detailed understanding of the structure and function of these proteins: hemagglutinin—[48, 289, 296, 295, 263], and neuraminidase—[42, 249, 188, 4].

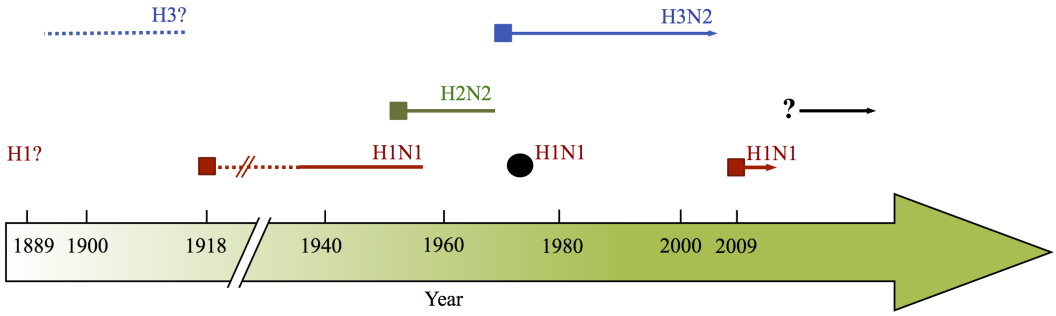


Figure 1: A timeline of influenza A viruses circulating in the human population in the last 100 years—three different hemagglutinin (H1, H2, and H3) and two neuraminidase (N1 and N2) subtypes. The solid square boxes represent the introduction of the pandemic strains H1N1, H2N2, H3N2, and H1N1 in 1918, 1957, 1968, and 2009 respectively (the major pandemics). The solid black circle represents virus strains introduced in 1977 thought to be variants of H1N1 subtype. The broken lines represent circulating strains based on serological data although the evidence is indirect. Source: Based on Palese's figure in [217, p. S83], but modified to reflect the 2009 H1N1 pandemic which exhibited traits similar to the 1918 virus and the uncertainty of the 1977 pandemic.

As can be expected, a person's immunity to the surface antigens reduces the likelihood of infection, and if infection occurs, reduces the severity of the disease [228, 67, 63]. Hence antigenic variation in the two glycoproteins drive the long-term epidemiological success of the virus. The variation occurs two principal ways—by antigenic *shifts* and *drifts*. In the first case, antigenic shifts describes a situation whereby the virus emerges with a new hemagglutinin segment in the human population and as such people lack immunity to the new strain and thus are susceptible to infection despite previous infection or vaccination. This shift may occur as a result of genetic reassortment between animal and human influenza A viruses, or between a progeny virus with a known virus in general circulation. The emergence of this new genetic hemagglutinin segment may take place with or without a new neuraminidase segment. The end result is a new influenza A virus subtype that has a high probability for rapid spread since most of the population lacks the needed immunity to the novel virus. Antigenic drifts on the other hand takes place via a variety of random mutations or 'drifts' to create different influenza A strains of the specific subtype. This drift is the virologic basis for the seasonal influenza epidemics we experience and the basis for the making of new vaccines to match the new strains that emerge.

2.2.2 Transmission, Signs, and Symptoms

Like most infectious diseases, influenza is spread directly when an infected person makes "adequate contact" with a susceptible individual [3]. For example, an infected person may expel the virus by sneezing, coughing, or even talking in the close proximity of a susceptible person [168]. The viruses enter the body through the mucus membranes of the individual's nose, eyes, or mouth [47].

It is important to note that not all signs and symptoms associated with influenza are caused by the virus. Some symptoms result from other secondary infections that may or may not be related to influenza activity. Hence, clinical confirmation is needed to definitely isolate influenza cases. As a result, the signs and symptoms are said to identify "*influenza-like-illnesses*" otherwise called ILL [204].

Many times, it is the complications from the infection that cause the second-order effects that increases influenza's morbidity and mortality rate. For example, pneumonia is the most commonly seen complication [205, 182, 39]. It can also worsen existing medical conditions such as asthma, heart, and other pulmonary diseases.

Transmission of the virus from the onset of infection time varies. *Viral shedding* (i.e., the virus leaving a cell) can take place as fast as a few hours from the start of the infection [47] or later [181]. The manifestation of the illness can thus be sudden. Generally, the incubation period is from 1 - 4 days with an average somewhere between 2 - 3 days [47, 100]. Others, however, think it is takes more time [114] [181].

2.2.3 Mitigation and Containment Strategies

When an emerging influenza epidemic that is of pandemic potential breaks out in the human population, different strategies are often employed to address it. The strategies involve a series of graded responses based on a 'subjective' assessment of the severity of the disease. For example, the responses could range from very limited interventions such as recommendations to wash your hands after contact with certain individuals to very firm responses such as travel bans and school closures in affected areas. In most cases, the decision makers are playing catch-up to the outbreak since not much is typically known initially about the

genetic composition of the emergent virus to develop and deploy appropriate vaccines.

In essence, the strategies are a combination of pharmaceutical and non-pharmaceutical measures [100, 101, 181, 114, 179, 125]. The first and best line of defense is vaccination (as an immunoprophylaxis) but vaccines are not immediately available because the virus is novel, and current stockpiles will most likely not be useful because there is a high probability that it will not be homologous-matched to the viral strain. Since a pandemic virus most likely emerged by an antigenic shift, it is difficult to predict the new hemagglutinin genetic segment of the virus hence difficult to produce a vaccine ahead of its emergence to match it. Typically, drug companies produce vaccines by selecting possible 'future' candidate viruses from the circulating pool, make the vaccines, and then stockpile them [248]. But because the viral pool is populated by strains largely from a genetic drifting process, the predicted strains have a high probability of not matching the pandemic strain. However, it may match the seasonal strain that evolved by a shifting process. Thus the development of a new vaccine is necessary when an outbreak occurs, but this takes time (may take up to 6 weeks after the incidence report).

Next in line of defense are antiviral drugs. They are considered the next best thing and are used for prophylaxis (for example, targeted at different strategic subpopulations [179, 181, 114]) and treatment (after infection). Like vaccines, antivirals (such as Tamiflu made by *Roche Holding AG*) are stockpiled as part of a national preparedness and containment strategy. However, the rationale behind this action has been questioned. Critics warn that millions of dollars may have been wasted on a drug that works no better than Acetaminophen or Tylenol [110]. They point out that the claimed "drug did not prevent the spread of flu or reduce dangerous complications, and only slightly helped symptoms," stoking a controversy of financial ties between the scientists who advised the WHO on the policy and the drug makers [2]. Also, the issue of resistance to antiviral drugs makes [175]. Essentially, stockpiling vaccines and antivirals for pandemic influenza controversial.

Finally, non-pharmaceutical interventions such as social distancing aimed as reducing contact, for example, school closures and travel bans, are deployed based on the need to

balance between impact and the cost of the socioeconomic disruption they may cause. Although much is yet to be understood regarding the dynamic patterns of human contact [49, 243], it is generally accepted that different environments and contact patterns affect the spreading of contagious diseases [82]. For instance, schools are particularly vulnerable because of the close concentration of young children who are often very susceptible. Consequently, school closures are commonly advocated in acute scenarios [117].

Symptomatic drugs such as over-the-counter (OTC) drugs that reduce the effects of some of the symptoms (e.g., coughs, runny nose, and headaches) are also used as a form of treatment, but they do not affect the progression of the virus so are not considered a major factor. In general, the accepted view is that vaccination in combination with antiviral drugs are the optimal tools to contain the spread [211].

Simulation studies suggest that the rapid activation of some of at least these plans can help arrest the epidemic development of a novel strain [151].

2.3 Modeling Diseases Spread

Modeling the spread of diseases at the population level centers around estimating the number of people that will be infected when an outbreak occurs, or more specifically, 'predicting' the patterns of spread that a disease will exhibit and their consequences. Modelers want to answer key questions like: How severe will an epidemic be? How has the disease been spreading through different populations? What is the time period between infection and onset of infectiousness? How many people will get infected? What will be the morbidity and mortality rates? How many new infections will each infected individual produce? Will current measures be enough to bring it under control? How should interventions such as antiviral drugs and vaccinations be deployed? And, how long will an epidemic last?

Traditionally, mathematical modeling has been used to answer some of these questions and has led to many fundamental ideas that have had significant impacts in epidemiology [153, 17, 10, 69, 109]. However, because of different research agendas and very real challenges such as numerical tractability, most epidemiological models are kept simple. As a result, they fall short in addressing real-life public health questions that have lots of complexity

such as human behavior, population heterogeneity, variations in the biology of both the virus and human hosts, and variations in human contact patterns. While the simple models are good for establishing broad principles, models that drive policy intervention plans need to include at least some of these layers of complexity.

The rapidly increasing availability of computational resources with very high computing power is now making it possible to incorporate some of these layers of complexity into our models to help us better answer some of the questions posed above. This has led to increasingly realistic epidemic models that leverage the availability of cheaper computational power and improved data (for example, highly detailed census and mobility data) to produce large-scale models that have been very useful for understanding the spread of a disease in large populations to improve mitigation and containment strategies [219, 5, 218, 125, 64, 191]. These computationally explicit models can now incorporate facets of the disease spread phenomenon with higher fidelity [86, 87, 89, 31, 15].

2.3.1 Disease Modeling History

The first application of modeling to the outbreak and spread of infectious diseases in a human population can be traced back to John Graunt's efforts to systematically quantify the causes of deaths in London presented in his book: *Natural and Political Observations made upon the Bills of Mortality* in 1662 [121]. In this book, Graunt analyzed the various causes of death published weekly by London parishes over a period of about twenty years and provided an imaginative yet systematic method for estimating the comparative risks of dying from the main killers. Essentially, Graunt outlined the concept of what is now considered as the "*theory of competing risks*" in modern epidemiology [69, p. 2]. Though Graunt's work was statistical and fascinating, it reached incorrect conclusions about the plague of 1636 by inferring that "...the contagion of the plague depends more upon the disposition of the air than upon the effluvia from the bodies of the men." Graunt did not rely on a mathematical model and also missed the idea of person-to-person contagion.

The earliest theoretical approach to mathematical modeling the spread of diseases was undertaken by Daniel Bernoulli in 1766. In his seminal paper [24], Bernoulli studied the

mortality due to smallpox and mathematically showed how many lives in a population could be saved if smallpox were eliminated as a cause. Ironically, Bernoulli's work had more immediate application in actuarial science than epidemiology[9] because it showed how to compute the gain in life expectancy in the context of competing risks [251, 71]. Bernoulli's novel work[10] led to the possibility of controlling smallpox by vaccination.

The first contributions to modern mathematical epidemiology is generally attributed to the work of P. D. EN'KO [78, 76] (nearly forty years before the Reed-Frost model which was not described until 1952 [3]). In 1889, he published in Russian a discrete-time model fitted to several cases of measles epidemics he observed in some closed boarding-schools in St. Petersburg. Another significant addition to modeling was done by Ronald Ross who developed the first mathematical model of malaria transmission in 1908, which drove modern theoretical epidemiology [238, 239]. Ross' model was cutting edge in that it embodied hypotheses of how the phenomena worked (i.e., of how the malaria parasite was transmitted). This work led to the possibility of managing malaria by controlling the vector population (i.e., the mosquitoes) and also won Ross the Nobel prize for medicine in 1902. This thinking of embodying hypotheses about how the world works into models of disease transmission set out a new path for how epidemiologists approached disease spread modeling at that time [189].

Building on works of Ross and others such as W. H. Hamer [127], McKendrick and Kermack published their seminal work, *A Contribution to the Mathematical Theory of Epidemics* in a set of three articles in 1927 [153], 1932 [154], and 1933 [155] that revolutionized the field. Their work had such a huge influence on the development of mathematical models for disease spread that they are still regarded as containing ideas relevant to contemporary epidemiology. The *Kermack—MckKendrick theory* was profound for three main reasons. First, it introduced continuous-time mathematics into epidemic modeling in a general way (built on McKendrick's work published the previous year [201]). Second, it proposed a model that accounted for how the '*age of infection*' (i.e., the time since becoming infected)

[9] Actually not until the survey article by [32] as noted by [77].

[10] It is worthy to note that scholars still continue to revisit Bernoulli's work 200 years after the publication reckoning that it still contains insights that have not yet been fully explored [80, 79].

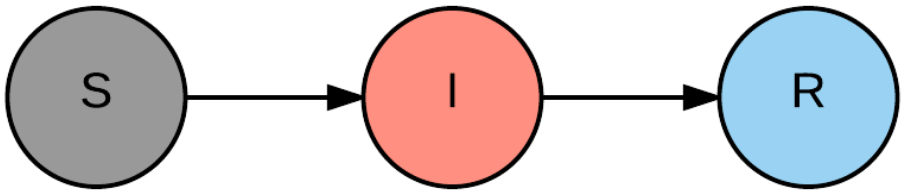


Figure 2: Schematic diagram of the classical *susceptible-infected-recovered* (SIR) disease model

affected disease transmission and recovery. This was an important concept that helped to improve model realism. Third, Kermack and McKendrick established the existence of a particular threshold number known as the *basic reproduction number* (R_0) for which large epidemics could only occur when crossed. The basic reproduction number is defined as the average number of secondary cases generated by a primary infectious case in an entirely susceptible population [10]. In a closed population, a disease can spread if $R_0 > 1$, but dies out eventually if $R_0 < 1$. Hence, R_0 can be used to critically characterize the spread of an epidemic and is used for this purpose in this dissertation.

Their model was a simple, compartmented, deterministic model where the population was demographically closed (i.e., no births or deaths allowed other than from the disease) and the population can be divided into three distinct compartments— the susceptible (S) compartment to contain healthy individuals vulnerable to the disease; the infected (I) compartment to contain individuals currently infected with the disease; and the removed (R) compartment to contain individuals that have either recovered from the infection and thus immune to secondary infections (caused by the influenza virus) or removed from circulation as a result of vaccination or death from the disease. For this reason, the model is generally called the SIR model. Figure 2 shows a schematic representation of the classic SIR model with these transition states. Many other variants of this basic model have since been developed to suit different needs. The reader can consult the standard texts for reference and application [10, 69, 17, 149].

Interest in modeling the spread of epidemics actually waned after the 1970's in favor of endemic diseases that were considered more prevalent and pressing. It was not until the severe acute respiratory syndrome (SARS) epidemic of 2002 - 2003 that interest in epidemic modeling was renewed [33]. SARS took us back to the Kermack–McKendrick model. Although the human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) epidemic spurred modeling interests in the early 1980's, its long timeline (i.e., incubation period) meant it could be modeled as an endemic disease with demographic effects.

After SARS, it was the threats posed by the spread of the avian flu of 2005 [273, 285] and more recently, the 2009 H1N1 influenza pandemic that spurred new interest in modeling the spread of epidemics and pandemics.

2.3.2 Types of Epidemic Models

There are generally two types of epidemic models—*deterministic* and *stochastic* models. The deterministic or compartmental models as they are also called are models in which the model output is exclusively determined by the model's history and input parameters. They are predictable models that produce the same output for the same given initial conditions. Most epidemic models in the literature have been deterministic. Specifically, most have been expressed by differential equations [69, 34]. Stochastic models on the other hand imply the presence of randomness and variable model parameters or states that are described by different probability distributions [11, 169].

Another set of deterministic models are the *spatial* models that show infection on a lattice [120]. This lattice or spatial approach takes into account heterogenous properties of disease spread such as correlations and clustering. Several forms based on different computational methods are possible here. For example, there are synchronous lattice models built using *cellular automata* [197], asynchronous models built using *monte carlo* techniques [74], and models built using *agent-based* computational techniques [85, 14].

Unlike the compartmental models, spatially explicit models allow us to add layers of

complexity into the model framework thereby providing us very high fidelity representational capabilities required for better public health interventions. These models can better depict realistic scenarios because they can include important features such as population heterogeneity and can offer the opportunity to trace down processes to the individual level. The future of population health modeling appears to be large-scale, computational spatial models for infectious disease spread [64, 5, 219, 191, 174].

It is important to recognize that no model is perfect. They can be used to forecast, but the results must be received with some caution. Because disease spread is a very complex process, it is not feasible to define a model with all the necessary parameters required to capture the disease spread process. Rather, models are tailored to specific questions, and consequently they vary widely. For example, two models A and B might be used to forecast the outcome of an epidemic. Model A may predict a casualty rate of 25% while B predicts 75%. The reason for this difference is that both models embody different underlying assumptions or hypotheses about how the real-world mechanism works. What is key therefore is to understand the data, the underlying ideas and assumptions behind the model, and the goals to be achieved. To state it in the apt words of Hethcote [135], there are "a thousand and one epidemic models" for every disease.

2.3.3 Agent-based Modeling & Applications to Policy

Computational models are powerful modeling and simulation techniques for capturing emergent phenomena resulting from the interactions of individual entities. Specifically, agent-based modeling is a system modeled as a collection of autonomous decision-making entities called *agents* that make individual decisions based on sets of rules [85, 14]. They are most effective when used in situations where complexity and uncertainty are constraints that need to managed in a multifaceted decision-making process. The complexities are features or attributes peculiar to agents in a heterogenous population and the uncertainties are choices or decisions to be made. In this modeling paradigm, neither constraint can be eliminated but only traded-of against the other.

While the use of agent-based modeling for empirical research is well established in the

sciences, its use in the social sciences, and in particular, the field of international affairs is far less known. Scholars in the field of international affairs who have used this form of inquiry include Cederman who showed how democratic states manifest their behaviors based on categorical traits of the agents. He did this using a series of agent-based computational models to trace complex macrohistorical transformation of actors [55]. Essentially, politically relevant cultural traits of the actors in different ethnic landscapes can be 'endogenized' societally and simulated to see how the social processes evolve, i.e., how they capture organizational domination and then dominate a territorial state. Another good example is Harrison's reflections on the credible uses of agent-based models in international and global studies [130]. However, this dissertation is about epidemic modeling and as such is focused on the application of agent-based models (ABMs) to disease spread. The interested reader can see Bruch and Atwell's study for a recent summary of the application of agent-based models in empirical social research [37].

According to Hammond [128], the use of ABMs to inform policy has its own peculiar set of considerations (i.e., processes and challenges). He classifies their use to inform policy into three specific "modalities" or distinct categories: *prospective*, *retrospective*, and *indirect* policy models.

Prospective policy models are models that help to inform the design of policies or interventions by clarifying the different potential impacts of those interventions on the phenomena under investigation. These models incorporate key features about the phenomena from the real world into the model along with explicit representations of policy choices the agents can take. The policy choices can be made within the system and compared. Essentially, they are 'in silico' experiments to understand the full potential consequences of interventions. Retrospective policy models are focused on helping users retrospectively understand the success or failure of a policy or intervention. In contrast indirect policy models are models that do not contain explicit representation of policies or interventions, but are rather aimed at helping users understand larger concepts such as etiology and bidirectional relationships between individual behavior of agents and the system structure over time. Models of infectious disease spread are typically framed as prospective models and

treated as such in this study. Examples of retrospective agent-based modeling in political science include works on party competition and bureaucratic policies [164, 165], and indirect agent-based modeling in the social sciences include the canonical work on the drivers of segregation [38, 300].

2.3.3.1 Application of agent-based models to infectious disease spread

Agent-based modeling is still relatively new to public and preventive health inquiries [183], but they can be powerful public health research tools because of their ability to depict how population-level behaviors emerge from different initial conditions (for example, different information and decision rules applied to different agents in the population). Initial applications[11] were focused on the epidemiology and control of infectious diseases [100, 101, 179, 178, 114, 303], but in recent times, the increasing availability of cheap computational power has stirred up interest in embedding more layers of complexity in such models to improve their realism [87, 219].

As part of the effort to increase the application of ABMs in public health inquiry, the National Institute for General Medical Sciences (NIGMS), a division of the National Institute of Health (NIH), funded a large network modelers to form the *Models of Infectious Disease Agent Study* (MIDAS) group to broaden its use for substantial scientific and policy impact [195].

In the next chapter, I review the state of the art in modeling spontaneous human behavioral changes in response to the spread of pandemic influenza and discuss the foundation of the modeling approach I adopt for this study.

[11] In perspective, ABMs have been applied to the spread of diseases in small town scenarios (population of 6,000 and 50,000 people [45]), large-scale urban cities (1.5 million people [93]), country scenarios [100, 101, 181, 114, 5], and at the global level [219].

CHAPTER III

HUMAN BEHAVIOR AND DISEASE MODELING

3.1 Introduction

Modeling the impact of human behaviors on the spread of infectious diseases such as pandemic influenza is a novel discipline, but one based on a rich history of traditional mathematical modeling[1] [153, 17, 10, 69, 109, 184]. Central to the modeling effort is how population heterogeneities affect disease spread [179, 126, 302, 99, 211, 100, 222, 175, 181, 109, 107, 29, 26, 89, 87, 301]. Particularly in the context of severe infections where large portions of a population are at risk, the implications of neglecting the interactions between a disease and society can be costly [192, 200].

Several approaches have been proposed to study these interactions [89, 87, 160, 108, 109, 222, 139], and they have led to increasingly realistic spatial models that have been very useful for understanding the spread of the disease in large populations allowing us to improve mitigation and containment strategies [219, 5, 218, 125, 64, 191]. These new models produce significantly better results than previous models and constitute the future of epidemic modeling. However, even these models lack adequate "behavior details" important for better model realism [87]. These current models focus on factors such as mobility-related effects [193, 18, 191, 93, 119, 156], which although important, do not adequately capture key population-level variables that may impact the spread of a disease. For example, variables such as people's *attitudes* towards the risk of infection and their *trust* in recommended health advisory information issued by the government to contain the disease spread [242, 89, 222, 145, 252, 139, 173]. When these features are incorporated into models, they may produce results that differ significantly from those models that lack them, and thus serve to enrich the debate on mitigation and containment strategies.

[1] It worth noting that infectious diseases are also modeled in the domain of Economics where they are called *economic epidemiological models* [113]. In this domain the focus is more on choices and economic analysis thus not examined in this dissertation.

In this chapter, I review some of the issues surrounding risk perception, trust, and pandemic influenza spread. Since the effects of risk perception on health decisions have been studied in the health belief model (HBM) literature [22, 141], I examine the literature for insights on frameworks that could be applied to modeling pandemic influenza spread. I also examine the literature on risk perception and pandemic influenza using the context of the most recent outbreak, the 2009 H1N1 pandemic to better understand some of the factors or constructs that modulated how people perceived and reacted to the risk of infection during the outbreak. Recent studies on this suggest that psychological constructs such as people's attitude and trust in the health advisory information disseminated by the health authorities shaped behaviors during the outbreak [252, 173, 43, 286, 240, 41]. To underscore the importance of the constructs, I examine reports related to the recent 2014 Ebola outbreak in West Africa to see if some of these constructs feature in the conversation since Ebola disease is considered similar to pandemic influenza (in symptoms, severity, and spread).

3.2 Health Belief Model Theory & Influenza Modeling

Health belief model theory [22, 141] is found in a suite of models based on decision theory and attitude-behavior constructs [83, 299, 102, 6]. It deals with behavioral changes with respect to prescribed health recommendations. HBM attempts to model the processes an individual uses to integrate recommended health information into the individual's decision-making processes. The goal is the adoption of the recommendations. Sometimes, this issue is also called the *patient adherence* problem[2]. Theoretically, HBM is probably one of the best of known frameworks developed to help us understand and explain patient adherence and has been used extensively to develop and improve intervention strategies. But HBM has been criticized as being "incomplete in its organization and development," lacking in robust validation, failing to clearly specify how the constructs involved are inter-related or should be measured, have modest support for patience adherence, and is thus not well suited for disease modeling [203, p. 439]. Especially for influenza, HBM is regarded as inadequate for predicting and understanding influenza vaccination behavior (a key factor in influenza

[2]The patient adherence problem is defined in literature broadly as compliance to prescribed medical interventions or advice, or enlisting patient cooperation to achieve therapeutic goals [28, 91, 276].

modeling) because it is missing important constructs that can help capture the motivations for influenza-related behavioral changes, and hence alternative models are suggested [203].

Others scholars such as [287, 58, 35] have also noted some of these limitations. Weinstein [287] challenged the validity or completeness of health behavior theories and posits that testing the theories can often be misleading. Chapman and Coups [58] emphasized that other constructs such as *worry* and *regret*, which are elements of emotions, are missing in HBM frameworks but can significantly affect influenza vaccination decisions. They found that the "ratings of anticipated worry and regret were stronger predictors of vaccination than perceived risk and mediated the effect of risk on vaccination" [58, p. 86]. So for instance, those who did not accept the influenza vaccine in the first year had high levels of worry and regret and were thus more likely to accept the vaccine the following year. Brewer et al. [35] pointed out that while constructs such as risk perception are central to many health behavior theories, the relationship between these core concepts and behavior is often not clear.

Weinstein and colleagues [288] actually examined the ability of several types of risk perceptions measures and other types of constructs from health behavior theories to predict influenza vaccinations. They found "anticipated regret" to be the strongest predictor of vaccination out of all the constructs they studied (included risk perception, worry, perceived vaccine effectiveness, as well as anticipated regret). Crucially, they noted that "risk perceptions predicted subsequent vaccination," but more so, a better predictor when this risk is "phrased in terms of feelings" rather than in purely cognitive terms [288, p. 146]. They pointed out that these theories are "missing some of the important determinants of vaccination and need substantial modification to explain this and perhaps other behaviors" [288, p. 151].

3.3 Risk Perception And The 2009 Pandemic Influenza

Seale et al. [252] surveyed a sample of residents in Sydney, Australia, during the 2009 H1N1 pandemic to determine among how the perceived risk of infection affected the likelihood of accepting the pandemic vaccine. They found that while most participants did not believe

they were at risk, slightly over half of the sample indicated their willingness to accept the vaccine. They concluded that *concerns* about vaccine safety were present and of serious concern during the outbreak and it impacted vaccine uptake. Others such as [139] found the perceived risks of infection and the precautionary behaviors elicited to be dynamic in time but differ geographically and demographically. In general, there is a similarity in the patterns of the precautionary behaviors exhibited in a population in response to a respiratory threat like pandemic influenza because the strategies for avoiding infection are few and specific [100, 101, 181, 114].

Liao and colleagues [173] also examined factors affecting intention to receive the vaccine in Hong Kong (N = 896 adults) and found similar concerns in their longitudinal study. Interestingly, they examined the decision-making scheme used by the general population using a modified Theory of Planned Behavior (TBP), one of the HBM theories. They collected data before and after the vaccination and examined the data using their modified TBP. They found among other things, that "perception of low risk (60%)" to the virus and "concerns regarding adverse effects of the vaccine (37%)" were the primary reasons why only 11% of the people that indicated intention to receive the vaccine actually got the vaccine. They concluded that people's perception of low risk of infection from the virus and high risk of adverse effect from the vaccine inhibited vaccine uptake. They pointed out that "intention alone" is not sufficient to predict future uptake rates because other proximal determinants such as vaccination planning played more significant roles.

Essentially, there is a lack of theoretical work in this domain investigating risk perceptions and protective behaviors, and more so, a lack of modeling studies. Leppin and Aro [170] reviewed several theoretical models and concepts (28 empirical studies from which 30 articles were published between 2003 and 2007) underlying current empirical research on pandemic influenza risk perception. They found that the concepts of risk perception discussed in the papers were mostly heterogeneous and used more in a "pragmatic than theory-based sense" [170, p. 7]. Risk perception was not conceived completely as a cognitive, or cognitive and emotional phenomenon, but a mix of both mediated by varying levels of expectancies.

Other scholars have also addressed this lack of theoretical framework. Bish and Michie [26] reviewed relevant literature with references to SARS, Avian, and Swine Flu pandemics and selected 26 papers they considered useful to describe conceptual frameworks that could help us better understand perception and protective behaviors. They also found that most of the studies "lacked an explicit theoretical framework." Majority of the studies they reviewed were not model-based and thus not predictive (in fact they commented that most of the studies were cross-sectional in nature and so could not be predictive anyway). While they noted demographic differences in the adoption of behaviors, it did not significantly affect their conclusions. Their key findings were thus: that perception (measured as two constructs—greater levels of perceived susceptibility to and perceived severity of the diseases) and belief (measured as a greater belief in the effectiveness of the behaviors recommended) are important predictors of protective behavior. What they termed "belief" is essentially a trust in the information released by health authorities. In fact, they highlighted that "greater levels of state anxiety and greater trust in authorities are associated with behavior." This hints at the notion of trust in information as an important construct of risk perception.

3.4 Conceptualizing Trust in Information, and Disease Spread

The concept of trust is studied across many disciplines such as political science, psychology, sociology, international relations, organizational behavior and management sciences, computer science, and even more recently social media. However, there is a lack of convergence on its definition and measurement across these disciplines. This is because there are different concepts of trust applied in different categories, such as to individuals, governments, and institutions. Thus there is a vagueness that pervades research on trust posing key challenges for researchers seeking to advance knowledge in this domain [129, 136, 138, 254, 167, 283].

In the social sciences, researchers have been unable to ascertain robust predictors of trust or confidence in government and have been using different forms of behavior as proxies. The narrative common to them all has been that trust in government and confidence in institutions has been declining since the 1960's [65, 212, 231, 198, 198], in line with current

opinion polls conducted by the Pew Research Center [148] and Gallup poll [111]. However, this does not mean an abandonment of the system, rather the existence and rise of skepticism [65]. Even in medical contexts where patients are expected to trust their physicians and medical institutions, no commonly shared understanding exists, and where it does, not much is known about the factors that affect it, and the behaviors it fosters [190, 124]. These vagueness has led to a proliferation of concepts, definitions, and measurement inconsistencies across multiple fields leaving much to be understood on trust and thus one of the chief problems in the field [16, 21]. Further more, others such as Bauer view trust as external to the actual trust desired—more as "an expectation based on thought processes and emotions" thus external to the concept of trust itself [21, p. 7]. This expectation is purely subjective and varies from person to person as different individuals place different values on the different factors that modulate trust.

Despite the lack of a robust theory on trust, the general sense is often framed in a three-place predicate form A-B-X where the element A (the truster) trusts B (the trustee) based on a subjective estimation (or beliefs) A has of the trustworthiness of B. Consequently, this influences A's display of relevant behavior or strategic consideration X towards B [16, 21]. In this dissertation, I focus on trust in the simple general active sense without adducing evidence to the reasons. In this simple sense, the trust once assumed does not evolve. So when I assume A trusts B, the trust does not vary.

However, variations exist in the expectations even when individuals receive the same signal. For example, different individuals (trusters) can receive the same signal from a trustee and yet have different estimation of the signal, leading to different levels of trust, and thus they behave differently towards the trustee. For Bauer [21], trust is an expectation and not a decision or behavior. Hence trust here is different from theories like expectation utility theory [280, 103] and prospect theory [144] often used as a basis for trust. The relationship of trust is even more complicated, when sentiments that affect vaccine uptake are involved [41]. In general, trust is difficult to operationalize and measure, at best it is vague or misapplied where defined [75, 264, 21].

3.5 Insights From The Recent Ebola Outbreak

The *Ebola virus disease* like other hemorrhagic fevers is a viral disease that can easily transmit from person-to-person causing illness and death on a large scale when severe [245]. Like pandemic influenza, homologous-matching vaccines are not immediately available and there is no known cure. Those infected with the virus essentially have to wait-out the virus actions within their bodies [97]. There is also a lack of modeling tools as part of the containment strategy for another outbreak. This could be because the disease was viewed in the past as an African problem, thus of less global concern [229]. However, the most recent outbreak which occurred in 2013 (to 2015) has changed that view as it became the most widespread epidemic of the disease in history. As a result, the World Health Organization now considers this latest outbreak in West Africa an international emergency that constitutes a global health risk (the worst in history and the most severe in the last 40 years) that deserves the same kind of response like the 2009 H1N1 outbreak commanded [150, 56].

Insights from news reports about the disease suggest that people's attitudes and trust in information about the disease played significant roles in shaping behaviors adopted during the outbreak. Keating suggests that "an effective response to a problem like Ebola requires public trust of authorities in the midst of a terrifying situation" [147]. Essentially, a large number of the population did not initially trust the government health advisory information (on protective measures to take) during the early stages of the outbreak in a number of the affected countries. For instance, noticeable levels of distrust was reported during the Guinea outbreak [210]. In fact, the Executive Director of the African Center for global Health and Social Transformation (ACHEST) remarked in observation that a "trust gap has developed between the health system and the general population which has made control efforts difficult in West Africa." He crucially noted that "the single most important lesson we learned was that building and holding public trust by the government and health personnel is the foundation for all control efforts" [214]. Trust in government information on protective actions to take during a severe outbreak of an infection like pandemic influenza or Ebola as in this case is an important factor that should be incorporated into pandemic influenza

behavior-disease models.

3.6 Summary

In this chapter, I discussed disease models that incorporate human behaviors, and focused on pandemic influenza. I discussed the importance of modeling as part of the preparedness and containment planning efforts, highlighting that it serves as an important tool to help us better understand the spread patterns of the disease and potential "tipping points" in the infection trajectory—such that when crossed, the outbreak becomes a major disaster [116, 177].

To gain a better understanding of how to incorporate behavior into influenza disease models that underscore the importance of the role of risk perception, I examined the HBM literature for insights on possible theoretical frameworks. I found that there was a lack of a theoretical framework in this domain investigating risk perceptions and protective behaviors [26], and more so, a lack of modeling studies [170]. I also highlighted the importance of the concept of trust in this context and examined its role in the 2009 H1N1 influenza pandemic and the 2013 Ebola virus disease outbreak for some insights. I found that trust (in the health advisory information disseminated by the government), though discussed and treated in many disciplines, is difficult to operationalize and measure. At best it is vague or misapplied where defined [75, 264, 21]. In spite of the modeling challenges, risk perception and trust in information are important constructs that should feature in pandemic influenza disease models [286, 240, 160, 225, 252, 288].

CHAPTER IV

A NEW COMPUTATIONAL EPIDEMIC FRAMEWORK — MASSAPIS

This chapter describes a computational framework and model, *Multi-Agent Simulation System for Analyzing Pandemic Influenza Spread* (MASSAPIS), which is capable of modeling individual social behaviors in the context of an outbreak of pandemic influenza for the purpose of policy analysis. The model has been built to investigate the spread of pandemic influenza A(H1N1) virus[1] in the U.S. population simulated using a synthetic population of 281 million individual agents. The framework can be used by decision-makers to simulate different outbreak scenarios to examine how the factors impact the disease spread dynamics. For example it can be used to model how factors such varying levels of disease severity (measured by varying the basic infectiousness rate, R_0), population size, demography, and interventions to contain the disease (vaccination and social distancing/school closures) impact the spread of the disease in the population.

MASSAPIS extends Parker and Epstein's GSAM framework [219] by (i) endowing agents with two psychological constructs—attitude and resolution, to capture how agents' attitudinal preferences and response to information about the risk of infection during the outbreak affect disease spread; (ii) implementing three new additional protective features to represent behavioral responses in the framework (vaccination, social distancing, and school closure); and (iii) enhancing the graphical user interface with new menu options and features to provide more functionality for MASSAPIS.

MASSAPIS is a multi-threaded stand-alone application written in the JAVA programming language[2] to be run on a 64-bit processor computer with at least 16 Gigabytes of Random Access Memory (RAM). The model is controlled using a Graphical User Interface

[1] Sometimes abbreviated as pH1N1 or the Swine Flu virus.

[2] Last implemented on Java version "1.8.0_65." Java(TM) SE Runtime Environment (build 1.8.0_65-*b*17).

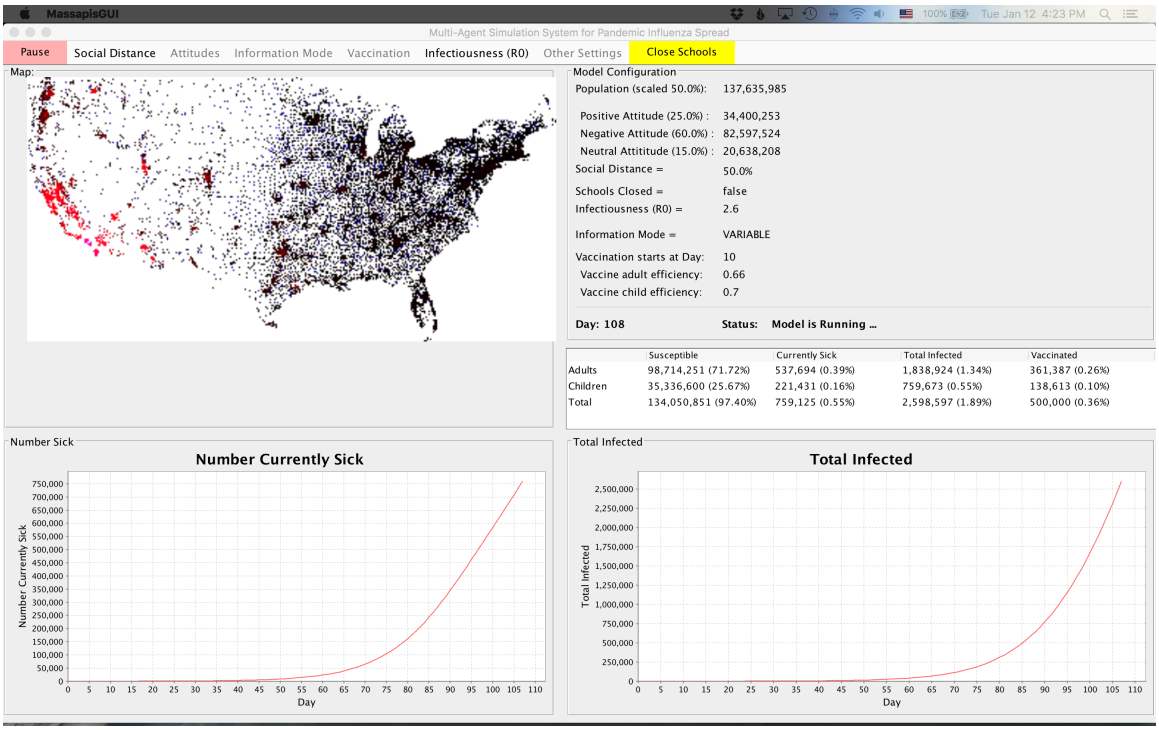


Figure 3: A screenshot of MASSAPIS application GUI in operation. The map showing the spatial spread of the disease is in the upper left-hand corner. The dashboard showing run-time statistics is in the upper right-hand corner while the charts showing the number of agents currently sick with the disease and the total infected are in the bottom half.

(GUI) shown in Figure 3.

The descriptions in this chapter include the structure of the framework and some essential components and functionalities that constitute the system. The focus here is more on providing a description of the model. Although the model is built on the U.S. population, it may be generalized for other synthetic populations in the future. The results of the simulation will be described in Chapter 5.

4.1 Framework Architecture

The system architecture of MASSAPIS is depicted conceptually in Figure 4. The key software modules that constitute the GSAM on which MASSAPIS is built are included in this diagram for completeness (shown in the gray area).

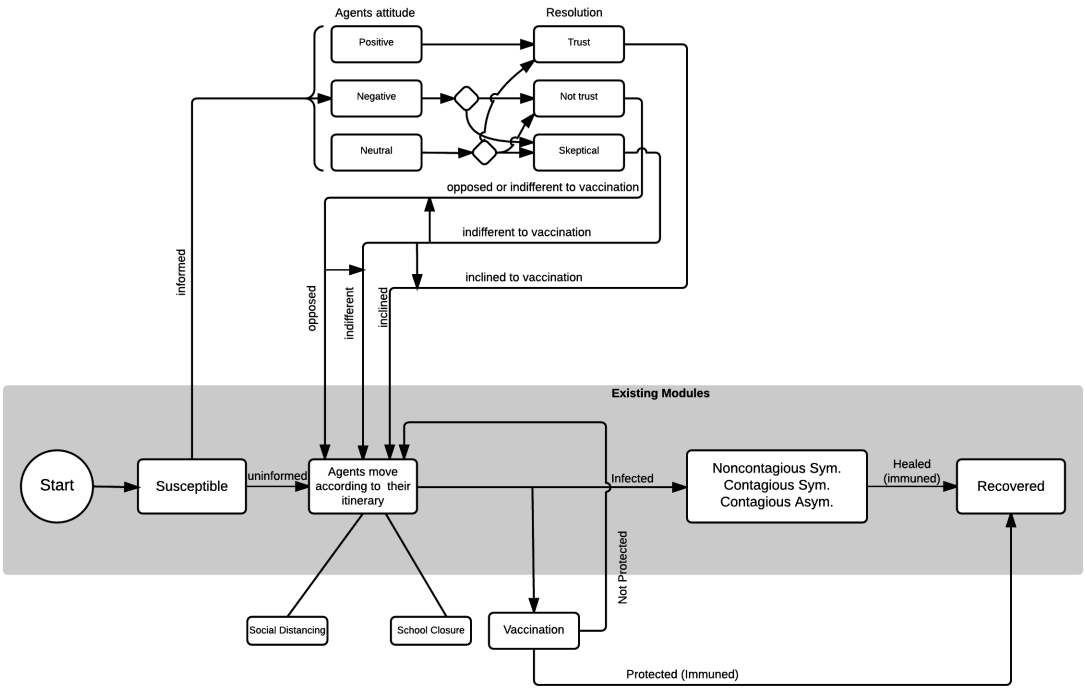


Figure 4: The system architecture of MASSAPIS showing the major software modules of the framework. The modules that constitute the GSAM are shown in the shaded area while the extension modules are shown outside of the shaded box. At the start of the simulation, all agents are susceptible to the disease. Depending on the mode at which the framework is operated, the model can be simulated in a configuration where agents in the model are either uninformed, become progressively informed (as the simulation proceeds), or fully informed (as at the start of the simulation) about the protective health measures to take to prevent the infection. When uninformed, the model simulates like the base model on which it is built (GSAM model), and when informed, the model simulates as MASSAPIS using the extended features.

4.1.1 Conceptual Model

A conceptual mapping of MASSAPIS is shown in Figure 5. It is made up of the core behavior module which represents software components that determine how the system operates (as GSAM or MASSAPIS) and thus exhibit its preventive behaviors, the agent itinerary behavior module which encapsulates social distancing and school closure methods, the population generator module that generates the synthetic population used for the simulation, the event recorder module which tracks all the disease events for proper house-keeping, and the visualization module which generates the simulation results graphically. Description of the modules are given below.

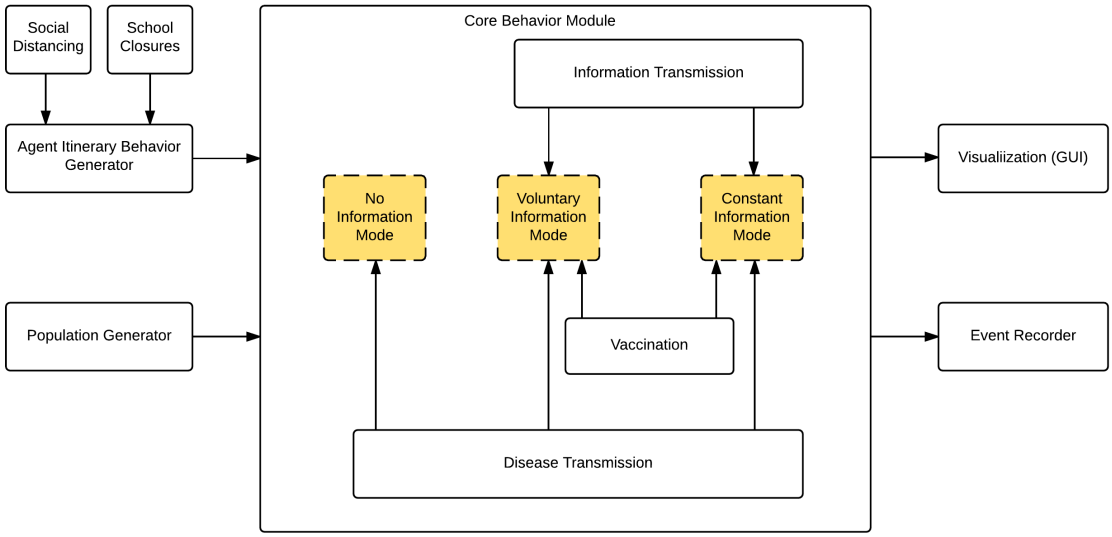


Figure 5: A conceptual diagram of MASSAPIS showing the key functional software modules. Central to the framework is the mode of operation (Information Mode) in which the model is simulated. The model can be simulated in three modes—No Information, Voluntary Information, and Constant Information — which determine model results. Information transmission and vaccination are only available when the model is run in either the Voluntary or Constant Information modes (functioning as MASSAPIS), while the model functions as the underlying GSAM model when operated in the No Information model.

4.1.1.1 Core Behavior Module

The core components representing the system behavior are logically grouped here for ease of understanding. The components are responsible for the following processes: disease transmission, information transmission, vaccination, and the information mode (i.e., the mode of operation) for the framework. The components are described below.

Disease Transmission Process

The same disease transmission process used in GSAM is incorporated into MASSAPIS. For ease of understanding, the disease model may be imagined as emulating the typical deterministic susceptible-infected-recovered (SIR) model [153, 10]. A schematic depiction is shown in Figure 6.

Diffusion of the disease is simulated by changing the infection status of every individual agent over the simulation time according to preset probabilities. The progression of the infection is governed by the natural history of the disease. The natural history of a disease (sometimes called the *disease states*) refers to the progression of a disease in an individual over time in the absence of treatment—that is, from its pathological onset to manifestation of the disease in the host individual to its eventual resolution (complete recovery or death) [46]. In this case, infected agents recover from the disease after progression and become immune to it and are thus removed from the population (recovered state). Vaccination is also implemented where application of it changes the disease state of agents from susceptible to recovered.

Six disease states are identified and modeled in the GSAM framework to represent the disease transmission process for pandemic influenza A/H1N1. The disease states are:

- the susceptible state,
- the infected state which consists of four states that are not necessarily sequential (*Noncontagious-Asymptomatic*, *Noncontagious-Symptomatic*, *Contagious-Asymptomatic*, and *Contagious-Symptomatic* states), and
- the recovered state.

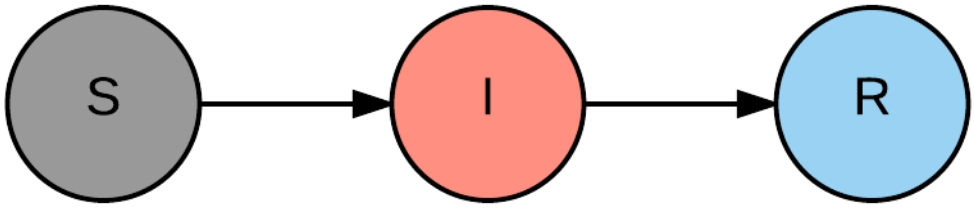


Figure 6: A schematic representation of a typical $S - I - R$ model. All members of the population are initially susceptible (color coded as black). Then on the onset of infection, some get infected and move to the infected state (color coded as red). Over time, infected agents transition to the recovered class and are removed from the population for disease transmission purposes (color coded as blue).

The four infected states are defined as follows:

1. NonContagious-Asymptomatic: Here infected agents are not yet able to transmit the pathogen (noncontagious) and also do not show the symptoms (asymptomatic). This means infected agents cannot yet infect or affect other susceptible agents in any way during contact. The agent can thus be considered as 'inactive[3]' in the model just like other susceptible agents. These agents cannot yet influence the epidemic results. This useful feature is used to reduce some of the computational overhead during simulation.

2. NonContagious-Symptomatic: In this state, agents are infected but not yet able to spread the pathogen. However, they show the disease symptoms. This means that although they cannot yet spread the disease, they are still able to affect others because they show the symptoms. When other susceptible agents see these symptoms they may be influenced to take precautionary steps such as limiting contact to minimize their own risk of exposure to the disease.

3. Contagious-Asymptomatic: Agents in this state are able to spread the virus (contagious) but do not show the visible symptoms (asymptomatic). Thus they are 'silent

[3]Agents are considered active if they are either contagious or symptomatic or both because they can infect or affect the behavior of other agents.

spreaders' because they do not signal to others (susceptible agents) their true state yet they can infect them on contact.

4. Contagious-Symptomatic: This is the state where agents spread the virus and also show the symptoms of the disease. Susceptible agents are able to take appropriate precautionary action because they can 'see' the true state of the infected agent around them and can take steps to avoid them if necessary.

To better understand the infected states, it is helpful to mention here that in general, the progression of an infection through a human host can take two paths or timelines differentiated by the ordering of their latent and incubation time periods [10]. When a host gets infected, the host does not immediately show the symptoms or transmit the pathogen—this is done over a period of time dependent largely on the host biology. The time it takes for the host to show the disease symptoms is called the incubation period (asymptomatic state) and the time it takes to become contagious is called the latent period (nonContagious state). The intensity of the infection is governed by its basic reproduction number, R_0 (defined in the next section).

The challenge is that there is no specific ordering of these paths. Either can occur before the other depending on factors such as how the pathogen interacts with the host's biology, presence of pre-existing pharmaceutical interventions, and so forth. The infected host may show symptoms (symptomatic state) before actually becoming contagious (contagious state) and able to infect others, or the host may become contagious first, infecting others well before showing the symptoms. On average, agents in the population get contagious about 2.1 days after infection or symptomatic about 1.9 days after infection. Infected agents transition through the infected states in about 4.1 days on average after which they recover. These numbers closely approximate the values others used for similar simulations. For example, the studies led by Ferguson [100] and Longini [181] show similar results. The actual details of how agents in the model transition through these six disease states has already been discussed in Parker and Epstein's work [219], thus it is not repeated here.

At the start of the simulation, all agents are set in the susceptible state. The disease

is then initialized by randomly infecting a select number of agents to start the infection process. This represents a scenario where the pandemic influenza virus 'reaches' the U.S. population facilitated by some external agency like air travel [278, 88]. I randomly selected 40 agents in the location with the highest population density (in California) and infected them with the disease to start off this process. This number of agents is close to what others used to initialize their model. For example, the Ferguson/Burke model of pandemic influenza spread in SouthEast Asia seeded 12 agents with an infection [100]. This number of agents to infect can be varied from the *Other Settings* menu in the application GUI toolbar (shown in Figure 10).

Finally, agents transition to the recovered state either of two ways—(i) after passing through the illness (i.e., infected states) and recovering from it, or (ii) by avoiding the illness completely if they receive the vaccine that provides them with immunity (i.e., a direct transition from the susceptible to the recovered state). The simulation ends either due to herd immunity when at least 36.6% of the population has been infected or when the number of infected agents in the population falls to 5.

Basic Reproductive Number (R_0)

The severity or transmissibility (sometimes referred to also as the attack rate) of an infectious disease is determined by its basic reproductive number (R_0). This is defined as the average number of secondary cases generated by a primary infectious case in an entirely susceptible population [10]. A disease can spread widely if $R_0 > 1$, but inevitably dies out if $R_0 < 1$. Obviously, the disease can be contained if we can control its reproductive number. However, this ability is out of our hands and out of the scope of this research.

Transmissibility of the influenza virus depends on a number of factors such as susceptibility of the population, geography, population density, and even demographic factors which are difficult to incorporate into models. Thus, R_0 varies considerably among studies and pandemics [279, 12, 200, 199]. Lower reproductive numbers are typically used for seasonal

influenza epidemics[4] while higher numbers are used for pandemics[5]. For example, Longini et al. [179] suggest a moderately severe epidemic as one with $R_0 < 1.6$. Colizza et al. [64] suggest a nearly severe epidemic as one with $R_0 < 1.9$ and a very severe epidemic perceived as one with $R_0 \geq 2.3$. For the Spanish Flu (considered to be most severe influenza pandemic in modern history)—Chowell and colleagues estimated the reproductive number to be somewhere between $1.49 - 3.75$ [61]. The general suggestion from the literature is that the average basic reproductive number for the 2009 Swine Flu lies somewhere close to 2. This number can be set in MASSAPIS incrementally in steps of 0.2 between a range of 1 - 4 from the Infectiousness menu in the application toolbar as shown in Figure 7.

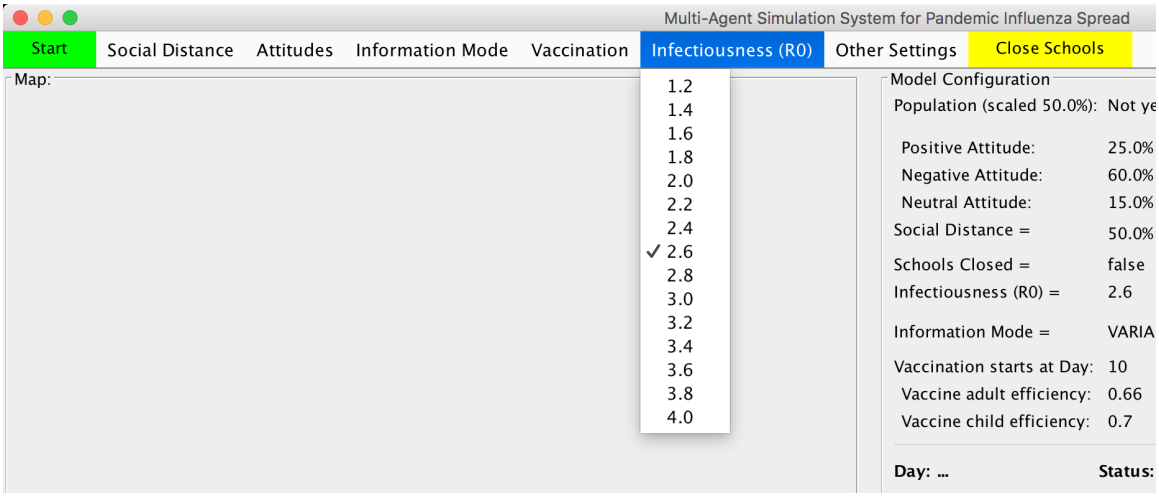


Figure 7: A screenshot of the application interface showing how to set the basic reproductive number for the simulation.

Other assumptions for the configuration include:

- Constant disease attack rate for both adults and children.
- 67% of infected agents develop influenza symptoms and 33% will be asymptomatic

[4]Note that the 2009 Swine Flu virus has not been totally wiped out yet from the human population. It is still present with us today but circulates in very low numbers with R_0 somewhere close to 1. It is one of the viruses that currently cause the seasonal flu, which may become an epidemic when $R_0 \geq 1$. It is noteworthy that when modeling at lower reproductive numbers, most epidemics seeded by a single individual generally go extinct by chance before becoming established in the population [100].

[5]In addition to using the reproductive number to make a distinction between an epidemic and a pandemic disease, it is often the origin of the virus that is an important factor. Typically, an emergent virus that causes a pandemic is of novel origin, as is the case with the 2009 Swine Flu. Often it is the antigenic drift that causes its emergence, which may or may not lead to a pandemic outbreak in the human population [112, 209, 303].

(similar to assumptions by others [181, 125]).

- Transmission is assumed to occur as follows - 30% in households, 37% in schools and workplaces, and 33% in the wider community. These are common mixing areas and parameters used in these kinds of studies [179, 181, 125, 100].

- Community transmission is considered to be a result of random mixing and modeled as localized random mixing with the risk of transmission determined by a power-law function as is typically the case in these studies.

- Weekend, seasonal, and other disease effects[6] are ignored.

Vaccination & Vaccine Effectiveness

Vaccination is a cornerstone and an effective preventive measure for limiting the spread of pandemic influenza [100, 101, 181], but its benefits are dependent on the disease dynamics[7], vaccine effectiveness, deployment time, vaccine supply, and uptake in the population [272, 19]. Since the GSAM lacked this capability, I built modules into the framework to implement a vaccination scheme in the population as part of my extension.

For this study, I employed a simple one-stage single-dose vaccination strategy based on the assumption that the vaccine is homologous-matched to the virus i.e., a single dose of the vaccine is applied to qualified susceptible agents on one specific day during the entire simulation. The homologous-matching aspect implies that the vaccine matches the genetic strain of circulating virus and is antigenically stable i.e., with no sign of genetic drift[8] [112]. Other studies have implemented a targeted vaccinated strategy where individuals or groups at higher risk of infection, for example, the elderly (over 65 year olds) and school-aged children (under 12 year olds) in the population are prioritized and vaccinated first [93, 125, 256].

[6] In reality, a spectrum of disease severity occurs during a pandemic. Neglecting all of these effects helps simplify modeling efforts.

[7] The disease dynamics includes among other factors multiple introduction of the disease into the community, disease viral strain type, and unpredictable host-disease interaction.

[8] Annual influenza epidemics occur partially due to strains of influenza genetically drifting from year to year. So vaccines are produced targeting the strains that are predicted to circulate before the coming season. However, a major antigenic shift can occur suddenly resulting in a pandemic [42].

For computability reasons, I assumed the single dose will provide the needed protection immediately when it is received and will provide immunity for the duration of the simulation. In reality, determining the number of doses and the duration of protection provided can be challenging because vaccination is typically provided to the population over an extended period time often in more than one dose. Also, immunity typically builds over time and can vary from person to person [42, 272]. For example, Fergusson et al. [101] assumed a single dose vaccine gave protection for two weeks and reduced susceptibility by about 70% in their model. Yang et al. [303] assumed two doses of the vaccine would be needed with at least three between the first and second doses in their study. However, they suggested that one dose could be sufficient for people over nine years old. Khazeni et al. [157] assumed that their vaccine would provide complete immunity to 75% of recipients fourteen days after vaccination. The wide variation in the effectiveness and dosage assumptions makes comparison with other models challenging and complicates model validation.

Modeling the effectiveness of the vaccine is also challenging since it is based on complex interactions of the vaccine with the host biology, since in actuality, some of those individuals that were vaccinated still remain susceptible to the disease. Researchers typically use an efficiency factor in the range of 60% - 100% in modeling studies [298, 275]. For MASSAPIS, I used a vaccine efficiency factor of 60% for adults and 70% for children in the population. This vaccination feature can be set from the *Other Settings* menu in the application interface as shown in Figure 8. I assumed that the vaccine would be more effective in adults than children because It has been shown that the biology of the adults in the population would be able to hold the vaccine agent in their bodies better than the children who often need multiple doses to maintain their immunity (since I used a single-dose approach).

Prosser et al. [230] calculated the cost-effectiveness of the 2009 pandemic influenza vaccination program in the U.S. (predicting the costs and health outcomes using inactivated vaccine compared to no vaccination) and found, among other things, that vaccination for children and working-age adults during the outbreak was cost-effective compared to other

preventive health interventions but that the delays in vaccine availability substantially impacted the cost-effectiveness of the vaccination program. In summary, vaccination is a cost-effective intervention but the associated delays (for drug development and deployment) is inevitable and impacts health outcomes.

In practice, vaccine deployment initially suffers from development delays and limited production capacity [256]. Currently, I vaccinated just 30 million agents representing about 10% of the agent population a month after the first outbreak of the virus to mimic this limited vaccine availability and delay issues. Vaccination uptake observed during the 2009 outbreak was similarly low [27]. The reasons for this is beyond the scope of this work, however some of the reasons typically adduced include delays in the drug discovery and deployment [230, 303, 272] and people's attitude towards vaccination [172]. The general suggestion amongst epidemiological researchers is to vaccinate somewhere in the range of 10% - 90% of the population [220].

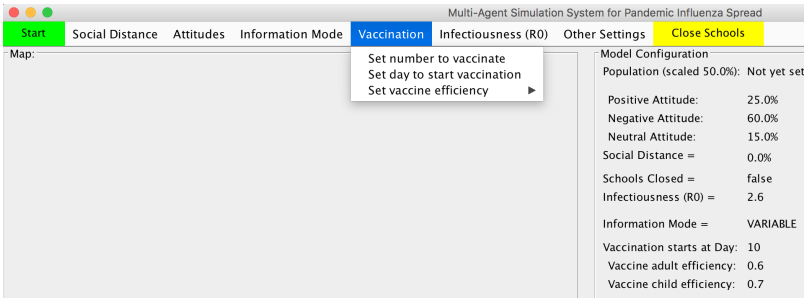


Figure 8: Vaccination menu from the application toolbar showing the options for how to: (i) set the number to vaccinate, (ii) the day to start the vaccination program, and (iii) the vaccine efficiency.

Information Transmission Process

Much of the conceptual framework which are use for understanding the diffusion of information in networks originates from the diffusion of innovation studies [237]. Contagion (disease or information) spreads from active (infected or influenced) to inactive (uninfected or uninfluenced) nodes (or agents) through in a network or population through some amount of contact. A rich set of models have been developed to examine different contagion mechanisms in different networks [57, 66, 171, 118, 236, 123, 208], but relevant to this study is the

generalization that information reaches a person in a network in two ways—through connections in one's social networks (implicit) and through external influences (exogenous) from out-of-network sources like mainstream media [208]. The effects of the external influences are often unobservable and difficult to measure.

In this thesis, I define information contagion as a health advisory or recommendation disseminated by the government agency responsible for coordinating the mitigation and control efforts during a pandemic influenza outbreak. This agency is considered to be the Centers for Disease Control and Prevention (CDC) in this case. I assume the information is disseminated through a range of media channels (for example, social media and mass media) constituting an individual's implicit and explicit networks.The importance of the mass media as the chief medium of information propagation is a good approximation here because information about pandemics are major national headline topics of discussion during an outbreak. Even healthworkers are tuned in to the mass media for directives in some cases. For example, Torun and colleagues [270] revealed that the media was the only source of information about pandemic influenza in nearly a third of healthcare workers they surveyed in a public hospital in Istanbul, Turkey, during the 2009 influenza outbreak.

While different advisory information is typically disseminated during a pandemic, I focus on the information type that encourages protective measures such as vaccination and social distancing. An example of this is quoted here:

> "Vaccines to protect against 2009 H1N1 are widely available. CDC is encouraging everyone to get vaccinated against 2009 H1N1. Those who have been patiently waiting to receive the 2009 H1N1 vaccine are now encouraged to get vaccinated. Due to early availability of, and high demand for, seasonal flu vaccine, remaining supplies of seasonal vaccine are limited. CDC continues to encourage those at highest risk from flu complications to seek seasonal flu vaccine and receive 2009 H1N1 vaccine, as recommended." – [53]

Because information diffuses alongside the disease in a complex way, it is difficult to fully represent the process in a behavior-disease model [89, 109, 98, 107]. Particularly in this age

of social media where we are increasingly interconnected with each other in intricate ways [60, 51]. In MASSAPIS, I conceived three modes of operation to govern how information diffuses in the model—the No Information, Voluntary Information, and Constant Information modes. In the No Information mode, no advisory information about the disease is disseminated and so agents are not enabled to respond with protective behaviors. Only the disease contagion circulates in the population, so the model simply functions as the GSAM base model. In the Voluntary Information mode, advisory information is disseminated in the system and diffuses like a contagion in the population over the simulation time. However, only those agents that are informed are enabled to respond to it. In the Constant Information mode, all agents in the model are informed at the start of the simulation and can thus respond to it right from the start of the simulation. The assumption in this case is that since pandemics typically emerges outside the U.S., the CDC and media would have had enough time to inform the entire population. As such, it can be assumed that every individual in the population would have already heard about it before the infection reaches the U.S. This is the mode used for two of the models tested in this experiment. The mode is selected from menu toolbar in the application GUI as shown in Figure 9 during model configuration.

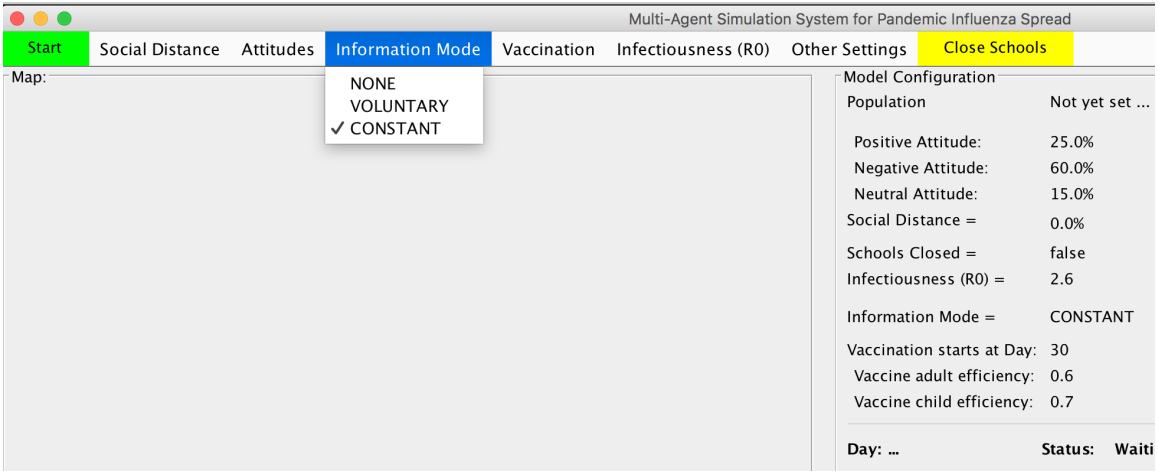


Figure 9: A screenshot of the application GUI showing how to set the Information Mode (i.e., mode of operation) for the system during model configuration.

The diffusion of information in the framework is modeled using a simple diffusion process.

At the start of the simulation, 100 uninformed agents are arbitrarily selected for infection with the information contagion to act as the initial spreaders in the population. The actual transmission process occurs either of two ways: (i) agent-to-agent contact made when two agents meet (implicit sources), and (ii) by randomly selecting an agent for infection to emulate an out-of-network 'media contact' (exogenous sources). For the agent-to-agent transmission, I assume an infection transmissibility probability of 20% as the effective contagion rate and a probability of 40% for the exogenous contact. The transmission probabilities though arbitrary, are below that suggested by Myers et al. for information diffusion in a network [208]. The parameters can be set and varied for analysis from the *Other Settings* menu in the application GUI toolbar as shown in Figure 10.

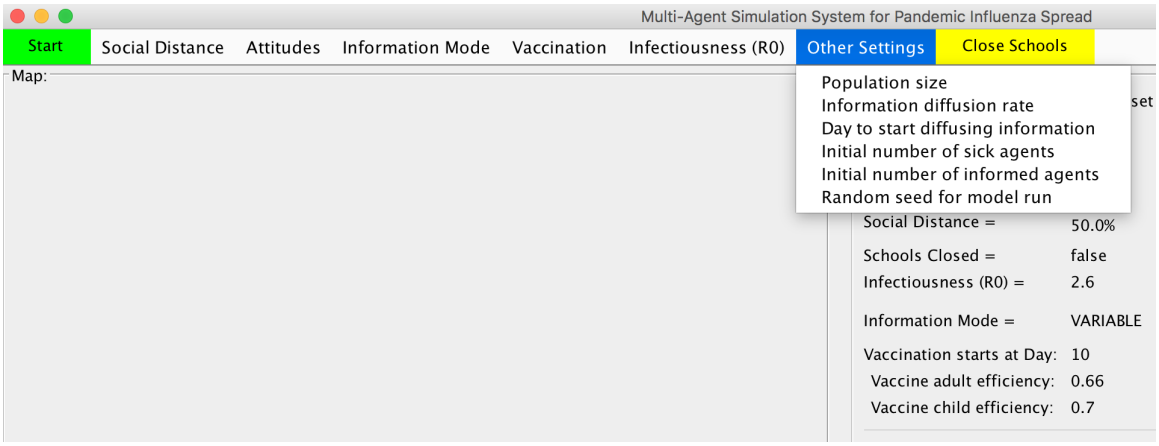


Figure 10: Other Settings menu items in the application toolbar.

4.1.1.2 Agent Itinerary Behavior Generator

The agent itinerary behavior generator is part of the GSAM module and adopted into MASSAPIS. It defines how agents move about their various social networks. The social networks are social groups that individual agents interact with as they go about their daily itinerary over the course of the simulation. Three contact groups are defined in the model consistent with typical assumptions—family, coworker/classmate, and random contact networks [101, 181, 178, 100]. For example, agents that belong to the same household are classified as being in the same family contact group.

Agent to agent contact is based on a probability of occurrence determined by the agents

itinerary pre-defined by the model designer. This probability is generated using a simple and efficient non-homogenous poisson process[9] to generate the time of the day (and hence the probability) at which the contacts will occur. This is an approach used by others in similar fast spreading disease scenarios [25]. The specific probability distribution implemented is depicted in Figure 11.

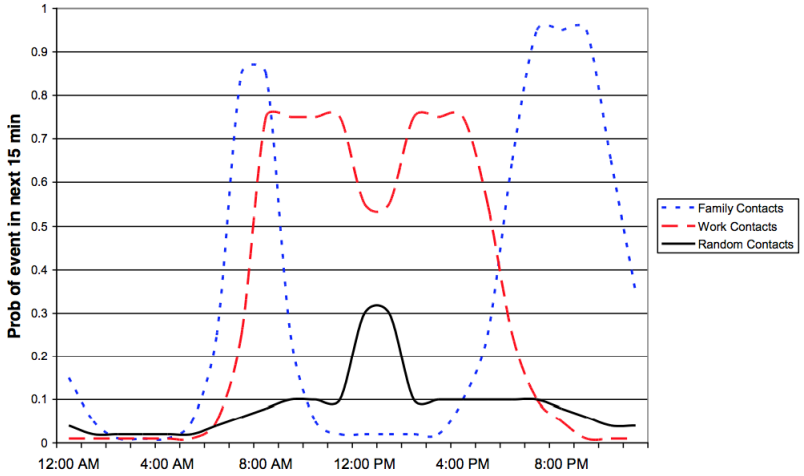


Figure 11: Diagram of the contact probabilities (referred to as behavior stream by Parker and Epstein [219]) for agents in the three contact groups embedded in the GSAM. This probability was generated by a non-homogenous poisson process. Observe that the probability of contact increases during the day time (around 9 to 5 PM) for work contacts and reduces for family contact as can be expected while the reverse is true in the evening time. Image source: [219].

Social Distancing & School Closures

Social distancing and school closure features are not implemented in GSAM and are part of the features I implemented in MASSAPIS. As previously described, social distancing and school closures form part of the recommended nonpharmaceutical intervention strategies for limiting the spread of pandemic influenza [101, 100, 181].

I implemented the social distancing scheme in this study by further limiting the contact probability of agents behavior streams. So for example, suppose an agent has a 60% probability of making contact with another agent in its social network, if the social distance

[9] A non-homogenous poisson process is suitable for modeling applications that generate random points in time [122]. For example, generating a probability for the number of people arriving at a specific location over time.

feature is activated and set to limit contact by 25%, then the updated contact probability will be $0.60(1 - 0.25) = 0.45$. The following limits are default values set in the framework: 25%, 50%, and 75%. For school closure, I implemented a scheme that prevents children-to-children contact when the school closure feature is activated. This simply checks the identity of agents during the contact and avoids contact when agents are school-aged and the school closure is turned on. Both features are configurable from the application GUI as shown in Figure 12.

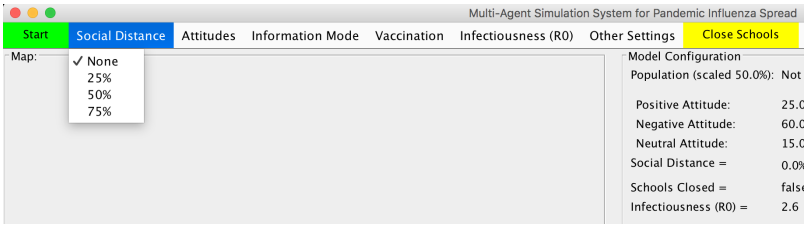


Figure 12: Snapshot of the application GUI showing how to set the social distance and school closure parameters during model configuration.

4.1.1.3 Population Generator

The population generator module is part of the underlying modules from the GSAM incorporated into MASSAPIS. The module generates the synthetic agents used to create the population simulated in the model, in this case, the U.S. population, based on a pre-defined dataset.

The population structure utilized is sized for the continental U.S. mapped to the Census Bureau data. Individual agents are approximately co-located in households constructed to reflect typical generational structure (for age and size). Households are randomly distributed with a local density determined by the LandScan population dataset[10] [163].

The dataset is a 43,200 by 20,880 grid of estimated population and agents are distributed onto the grid based on longitude, latitude, and zip code to approximate individuals co-located in households, schools, and workplaces. Demographically, agents are classified by age—as either adults (defined as individuals 18 years of age or over) or children (defined

[10]The LandScan dataset produced by Oak Ridge National Lab (ORNL) is a global population distribution dataset considered by many as one of the finest population data available. It is a model of instantaneous population density rather than population density and has a 1 km (30 in by 30 in) resolution.

as individuals under 18 years of age) and placed in households in line with the 2010 census data. As part of the enhancement to the base model, I added additional demographic markers for each of the agent in MASSAPIS: attitude, resolution, information status, and vaccination status.

The dataset consists of a population of 281.4 million agents. 74.4% are marked as adults and 25.6% are children. An average of 2.42 people are expected in households. These numbers are close to the latest Vintage[11] population estimates released by the Census Bureau (for 2014, 77% are age 18 or over and 23% are under 18 [274]). All households have a household 'head' that influence certain 'decisions' made by the children in the households. For example, if the head of the household is against vaccination, the children will also follow after this decision.

For computational efficiency reasons, the total population is partitioned into smaller more 'manageable' grids or *ModelBlocks* (MB) that aggregates agents that live in the same vicinity. For example, agents in the same zip code, city block, or square-kilometer area can be grouped together in the same ModelBlock. 27,500 ModelBlocks[12] (defined as 20 km-by-20 km grids) are contained in this platform. Therefore agents in the same ModelBlocks are more likely to interact with agents in their own ModelBlock reducing the communication burden and improving performance because the simulation can now run ModelBlock by ModelBlock instead of simulating the entire population at once. Agents in each ModelBlock are further partioned into smaller groups called *AgentGroups* to further ease computation. An AgentGroup contains about 1,800 agents when the full population size is simulated and about 900 agents when the population size simulated is reduced by half. Figure 13 shows a schematic outline of this population breakdown. Agents are identified as belonging to a specific AgentGroup in a particular ModelBlock and tracked (for communication and infection purposes) for the duration of the simulation. The population size can be scaled (i.e., reduced) as desired for computational efficiency purposes. The scale value can be set

[11] Vintage population estimates are revisions to the census estimates and are released by the U.S. Census Bureau each year. In this case, post-2010 estimates.

[12] MASSAPIS software application requires a computer with at least 8-core processors. The ModelBlocks are distributed between the 8 cores for multithreading.

from the Other Settings menu in the application GUI as shown in Figure 14 during model configuration.

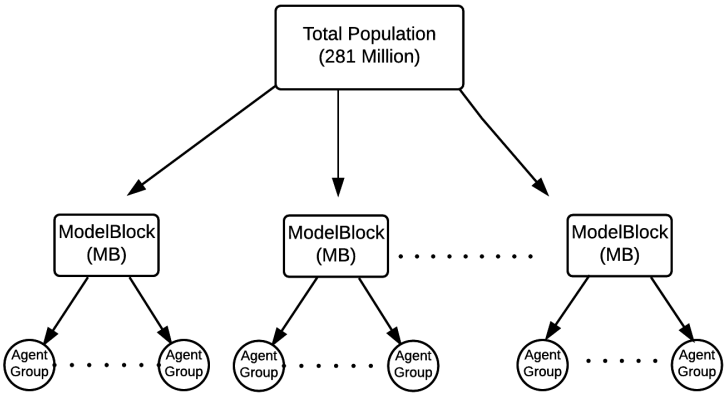


Figure 13: Schematic representation of how the agent population is partitioned into smaller groups called AgentGroups for computational efficiency reasons. The model is actually simulated sequentially AgentGroup-by-AgentGroup in the system.

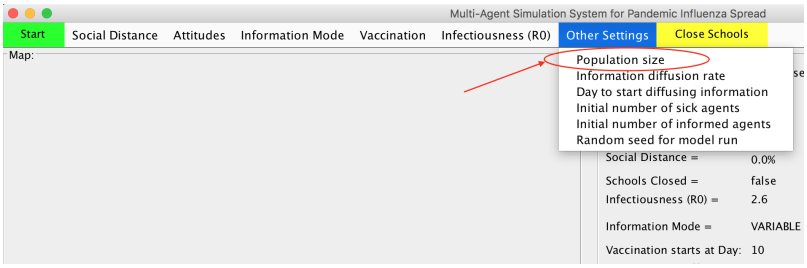


Figure 14: Screenshot of the application GUI showing how to set the population size from the menu toolbar.

4.1.1.4 Event Recorder

The event recorder module is part of the GSAM framework incorporated into MASSAPIS. It consists of components that record and track all the communication and disease state events of the agents during the simulation. For example, events like tracking the run time, agents' disease statuses, and their contact list during the simulation. The implementation details of this module can be found in Parker and Epstein [219].

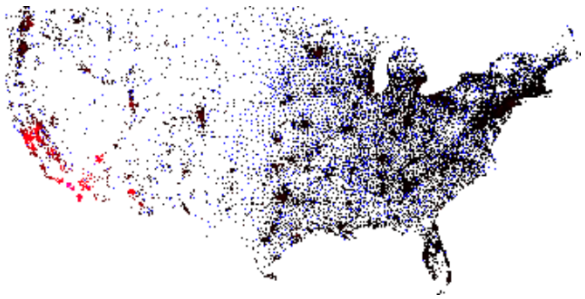
4.1.1.5 Visualization

The visualization module constitute all the components that make up the application graphical user interface (GUI). The application itself and the GUI front-end part are both built in Java as a stand-alone multithreaded application. I extended the original user interface to incorporate the additional features provided by MASSAPIS. The added features to the interface include an enriched menu toolbar used to configure some of the model parameters and a dashboard for displaying some of the model configuration parameters and results.

The interface also displays the disease states of agents in the model superimposed on a map of the continental U.S. and two charts (the number of agents currently sick and the total number infected) for tracking the impact of the disease in the population. A screenshot of the application GUI is shown in Figure 3.

As the disease progresses through the population, the color of the map tracking the disease states (located in the top left-hand corner of Figure 3) changes to reflect the intensity of the infection. The color of the map changes from black (signifying susceptible agents), to red (infected agents), to blue (recovered agents). This visual depiction allows users of the system to see the progression of the disease in the population for quick policy insights. Example screenshots of the progression is shown in Figure 15

(a)



(b)

(c)

(d)

Figure 15: Map showing the progression of the disease in the population at: (a) the start of the simulation; (b) around day 120 of the simulation run; (c) around the peak time of infection; and at (d) the end of the simulation. The black color represents susceptible agents, red represents the infected agents, and blue represents agents that have recovered from the disease.

4.1.2 Spontaneous Behavior Capability Features

The distinctive feature of MASSAPIS is its implementation of preventive behaviors in response to the perceived threat of infection during an outbreak of pandemic influenza in a population. Note that I use the term 'behavior' (or 'preventive behavior') differently than Parker and Epstein [219]. In the GSAM, the term behavior or behaviorstream is used to refer to the way the agents go about their daily itinerary within their social circles (see Figure 11). Essentially, a probability distribution of agent-to-agent contact in the three social circles defined in the model. Here, I use the term behavior to mean the attitudes, resolutions, and actions agents take in response to advisory information about the disease disseminated by the CDC (vaccination and social distancing). However, the term is loosely used in the literature to encompass different actions surrounding an intervention as well as the intervention agent itself. For instance, vaccination uptake is sometimes called "vaccination behavior" without considering the choices leading to the action [203, 244]. At other times, it includes the actions as well as the drug use [143]. I used the term in this latter sense mostly, but sometimes I also used it to apply just to the intervention agent.

The attitude and resolution attributes are conceived as a two-stage decision-making process used by informed agents to determine their course of action (see the framework diagram in Figure 4). The attitude is conceived like an intention to take an action, while the resolution represents the finalized intent. I used this approach to mimic the *intention-behavior* gap that is noticed between intentions and ultimate behavior [102, 7, 8, 261, 255, 137]. Expressed simply, an individual may possess an intention (or as in this case an attitude) towards a health behavior, but may end up not taking the action or fully carry it out to its logical conclusion. For example, Bish et al. [26] noted that a differential existed between intention and vaccination uptake during the 2009 outbreak. That is, not all individuals that declared an intention to take the vaccine went ahead with the commitment.

In the next section, I briefly describe how attitudes and resolutions work together to produce the behavioral changes modeled in this thesis. Note that these features are activated when the model is run in either the Variable Information or Complete Information mode as previously discussed.

Setting Agents' Attitudes

All agents in the model are endowed with an attitude attribute to capture their psychological preferences or 'intentions' towards the recommended preventive measures aimed at limiting infection. I modeled three broad categories—positive, negative, and neutral attitudes — similar to the three categories used by Mao [185] and Ormen et al. [215]. Agents with a positive attitude represent individuals in the population inclined to believe the health recommendation issued by the government advising them to adopt protective measures, topmost of which is vaccination. Agents with negative attitudes represent those inclined not to believe the information, while agents with neutral attitudes represent individuals who are undecided or ambivalent about the recommendations.

When agents make contact or acquire the information, they 'react' to it immediately (i.e, spontaneously) to form resolutions or the course of action to take. Here, three resolution attributes are modeled: The resolution to trust, not trust, or be skeptical about the information. The resolution process is depicted in Figure 16 for more clarity.

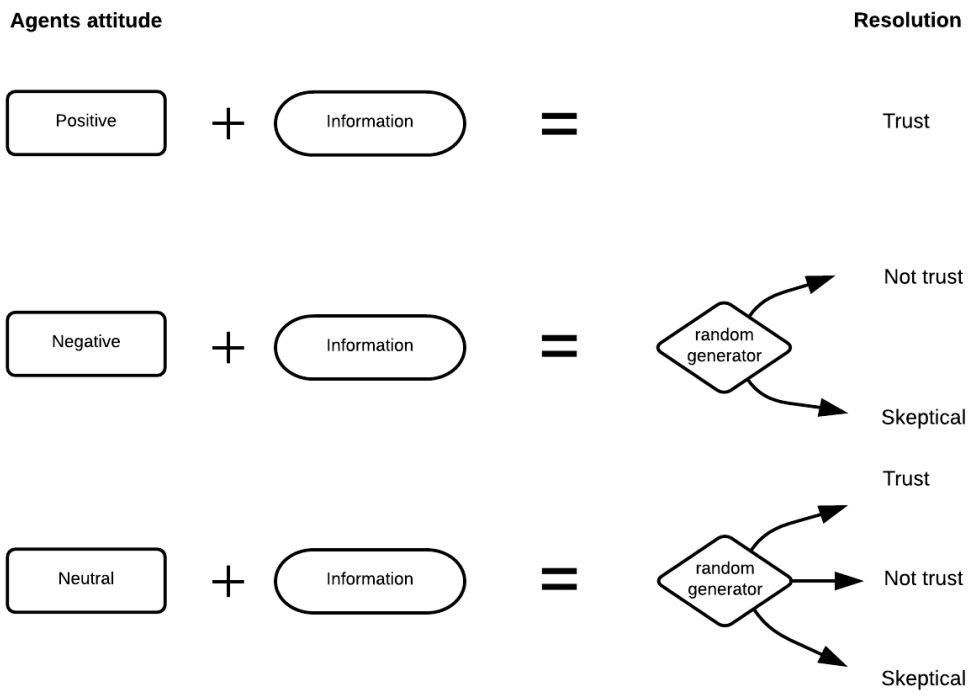


Figure 16: Schematic representation of agents attitudes interacting with information to form their corresponding resolutions.

Estimating the attitude parameters is nontrivial since it is a complex psychological variable and beyond the scope of this dissertation. For the sake of simplicity, I assumed the attitudes remain unchanged once formed by agents in this experiment. In reality, attitudes are non-static variables and evolve over time as an individual's knowledge and preferences change.

Studies examining vaccine uptake during the 2009 outbreak suggest that vaccine uptake was low and people largely did not trust the vaccine [27, 270, 29]. Consequently, I assumed a large percentage of the current population had a largely negative attitude towards the recommendation. I estimated this number to be about 60% of the population, and I assigned the other parameters as thus: positive attitude – 25% and neutral attitude – 15%. In reality, empirically determining estimating these parameters is fraught due to a lack of reliable data.

For the households with children in the population, I assigned the children the same

attitude as the head of their household so that they make the same 'choices' as the head of the household. So for example, if the head of the household had a positive attitude, the children present in the household will also be assigned positive attitudes. This is because parents to a large extent influence the vaccination uptake record of their children as observed during the 2009 outbreak [270, 215, 304, 27, 30]. The attitude parameters can be set from the application GUI as shown in Figure 17.

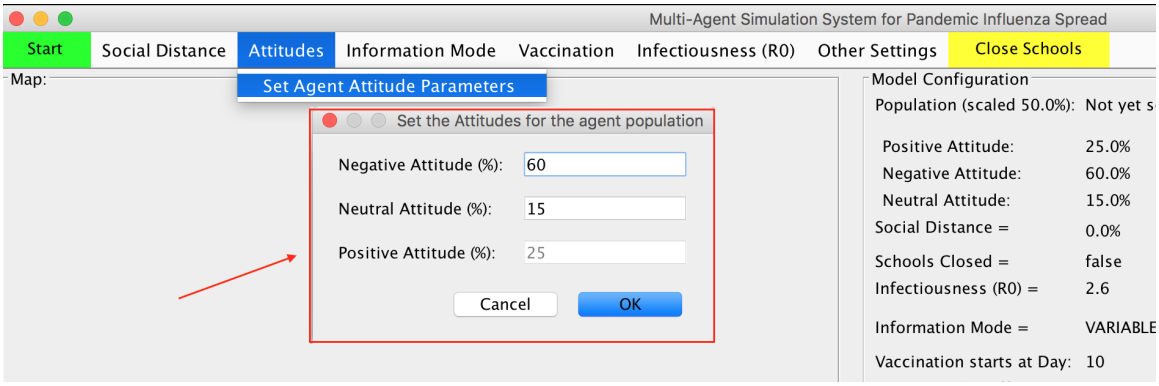


Figure 17: Screenshot of the application GUI showing how to set agents' attitude parameters.

Setting Agents' Resolutions

As previously highlighted, the resolution acts as the final intent of agents. It adds variation to an agent's attitude or first intention such that in some cases the final intention may be different from the initial one. For this experiment, three resolutions are assumed following from the three attitudes.

The resolutions are determined according to these rules:

- All agents that have positive attitudes when informed have a resolution of *Trust*. They trust the information and are inclined to accept the protective measures.

- Agents with negative attitudes when informed are randomly assigned to either of these two resolutions—*Not Trust* or be *Skeptical*. This assignment is done to capture the idea that not all agents with negative attitudes reject the recommendations. Some are skeptical but in the long run accept the recommendations even though they lack

conviction the recommendations are true. This duality was noticed during the 2009 outbreak [215, 27], and is represented in MASSAPIS using simple probabilities. In essence, agents that have a resolution of Not Trust are opposed to the vaccine while those that are Skeptical may accept or reject it.

- Agents that have a neutral attitude are undecided and are randomly assigned any of the three resolutions. As observed during the 2009 outbreak [270, 304, 27], some people did not outright accept or reject the idea, but maintained a 'middle ground' on the issue. They thus could be swayed to any of the three resolutions. Currently, I assigned such agents resolutions according to the following probabilities: Trust - 33%, Not Trust - 33%, and Skeptical - 34%.

Setting Agents' Vaccination Behavior

Three vaccination preferences are modeled in this work to represent individuals who are: inclined, opposed, or indifferent to the vaccine. Generally, those inclined receive the vaccine, those opposed reject it, and those indifferent may or may not accept it. Technically, the vaccination preferences are just the result of the resolutions but have the added feature of some variation added to it.

I configured the preferences thusly:

- Agents that have a resolution of Trust are all inclined to the vaccine and will accept it at the appointed time.

- Agents that have a Not Trust resolution have some variability added to their outcome because they are randomly assigned the following preferences— 80% are set to oppose the vaccine and 20% set to be indifferent to it. I used this variability to reflect the notion that a small percentage of those who do not really trust may relax their preference (for some undisclosed reasons) and accept the vaccine. This possibility to make that transition is offered by setting some small percentage of the agents as indifferent.

- Agents that are Skeptical are randomly assigned the following preferences—20% are

inclined, 40% are indifferent, and the remaining 40% opposed. The idea behind this is to reflect some of the variation in decisions that skeptical people manifest towards the vaccine [304].

Agents with an 'inclined' preference will always accept the vaccine, agents that are opposed will always reject the vaccine, and those indifferent may or may not accept the vaccine. The vaccine confers immunity and permanently removes agents from the infected class to the recovered class.

Varying Agents' Contact Behavior

In addition to implementing different vaccination behaviors, I also implemented a scheme to allow the informed agents to vary how they make contact with other agents as a means of limiting contact based on their resolutions. This is to enable informed agents to take steps to limit contact with other agents with a view towards influencing their infection profiles. This is a form of social distancing based on agents' resolutions. I formulated the following rules to implement the actions:

- For agents with a resolution of Trust, I limited their contact rate by 50%. This is because I assume that agents that trust the information will take preventive steps to reduce contact. I arbitrarily assumed this reduction in contact rate.

- For agents with a resolution of Not Trust, I arbitrarily increased their contact rate by 25%. I used this to emulate the notion that individuals that do not trust a recommendation will tend to take on more risk than usual. Thus, increasing their contact rate will increase their chances of getting infected thereby making them more prone to infection.

- For agents with a Skeptical resolution, I implemented a scheme that combines actions from the two previous steps. I configured 50% of the agents to limit their contact rate by 50%, 25% of the agents to increase contact by 25%, and the remaining 25% to maintain their current preset contact rates. Since skeptical agents are undecided, on a course of preventive action, I assumed that some of them may take the preventive

action, some may reject it and be more inclined to take risks that will expose them to more infections, and some will remain undecided taking no actions at all that will either decrease or increase their risk profile. Due to the difficulty of approximating these parameters in the real world, I used arbitrary percentages for ease of simulation.

4.2 Summary

In this chapter, I discussed the computational framework I developed called MASSAPIS, an exploratory tool designed for decision-makers to explore how certain spontaneous human behaviors impact the spread of pandemic influenza in the U.S. population for policy intervention purposes during an outbreak. MASSAPIS is an extension to the GSAM, thus inherits a significant part of GSAM's software code base. I presented the methodological approach that I employed to develop the framework, discussed its key components using a conceptual model, and highlighted its spontaneous behavior capability features. It is noteworthy that estimating the model parameters is fraught with difficulty due to a lack of sufficient data and studies to ground assumptions. Thus many assumptions are made to ensure computational feasibility and maintain parsimony. This is one of the perennial challenges encountered in modeling human behavioral responses and large networks [89, 98, 107]. Importantly, although MASSAPIS is currently configured for the U.S. population, it can be re-configured and applied to other populations for similar analyses.

CHAPTER V

RESULTS, VALIDATION, & DISCUSSION

In this chapter, I present the simulation results obtained from the models tested, the validation approach employed, and the implications of the results for policy insights.

I tested four models in this thesis—baseline, baseline with social distancing, largely negative attitude, and largely positive attitude models. The baseline model represents the case where the disease progresses in the population without any form of intervention (vaccination and social distancing), essentially, operating as the underlying GSAM model; the baseline with social distancing model approximates a population where individuals limit disease progression by social distancing alone without any drug intervention; the largely negative attitude model is configured to represent a population where individuals are largely hesitant of government-inspired preventive measures; and the largely positive attitude model represents a population where individuals are largely receptive of the measures. I simulated these four models using six scenarios of disease transmissibility to obtain results that span a range of low to severe disease infectiousness. I created the scenarios by varying the basic reproductive number R_0 as is typically done in these kinds of spatiotemporal studies [179, 114, 125, 101]. I varied R_0 in the range of 1.6 — 4.0.

Two main sets of results per scenario are obtained from each simulation—the *Number Currently Sick* (or current incidence) and the *Total Infected* (or disease burden). The number currently sick is defined as the number of symptomatic cases of the infection that occur daily while the total infected is the cumulative sum of the number of agents infected with the disease. Both measurements are recorded at each simulation time step and displayed graphically in the application GUI as shown in Figure 3.

It should be noted that the results reported are hypothetical scenarios and not 'predictions.' Scenarios are simply conceptualization of what could happen if certain conditions hold (i.e., based on what we know about the state of the system), while predictions are like

best guesses of what will actually happen given the conditions. This distinction is germane to avoid misinterpretation as policymakers and other consumers of these kinds of research are often interested in obtaining a 'single-number' estimate to use for decision-making. This study gives contrasting scenarios within the limits of the performance of the model for more insight into how a potent disease such as pandemic influenza A/H1N1 may spread in the United States. Provided that the assumptions are 'reasonable,' the model results may be taken as 'truth' but with consideration of uncertainty.

The model validation, results, and discussion of the results are presented in the following sections.

5.1 Model Validation

Validating agent-based models like MASSAPIS[1] empirically is fraught with many difficulties. Two challenges standout—first, the critical issue of software verification, and second, the many methodological challenges[2] that beset the validation of agent-based models [90, 196]. In the first case, representing the heterogeneities of agents and the complex interactions that may result (i.e., the emergence of new patterns of macro-level behavior) is difficult to verify and benchmark with other models. In the second case, the lack of appropriate and sufficient data to parameterize the model leads to many methodological challenges such as the making of arbitrary approximations for the sake of model simplicity [89, 98, 107].

As a result, the concept of validating agent-based models is generally not approached the same way as it is done in other domains. Other researchers have even suggested that the term validation as empirically conceived is no longer adequate as agent-based models capture many interactions not easily reflected in observed data. Instead, they suggest a

[1] It is should be noted that even the GSAM on which MASSAPIS is based was not validated [219, p. 4].

[2] Some of the other challenges include: (1) artificial societies are modeled differently by different researchers thus difficult to find a common basis for comparing different models, and (2) the features of the real societies which the agent-based models represent are subject to structural changes over time such that even within a single generation of observation, several model adjustments and recalibrations may be needed to maintain model fidelity. For example, the fall of the Berlin wall brought a sudden, comprehensive, and instantaneous change to the German society within a single generation of observation. So models representing that society used before the fall of the wall for population-level insights will need to be recalibrated to obtain 'valid' results after the wall came down.

more qualitative view of validation and use the term 'authentication' as it reflects more of forensic abilities and witnessing [23]. In general, validation of agent-based models is simply done either by comparing model results with each other or comparing the model result to some known ground truth. In reality, close connections with empiricists are needed to help validate these models so that the empirical results obtained can be better grounded in theory for explanatory or predictive purposes. A richer discussion on the alternatives and prospects of empirical validation of agent-based models can be found in [23, 297, 206, 94].

To validate the models, I compared the model results with the historical data of the disease burden as reported by the CDC. While this is a minimalist approach, it provides at least a reference point for assessing the models based on the impact of the disease in the population. The CDC reported that 60.8 million individuals were affected by the disease during the outbreak (April 12, 2009 - April 10, 2010) [257]. It should be noted that while the pandemic was contained within 12 months of the reported outbreak, the A/H1N1 virus strain that caused the disease still remains in circulation (at low-levels) in the human population even now and sometimes causes some of the seasonal influenzas.

5.2 Results

I created four models and tested them for six scenarios of disease transmissibility set at R_0 = 1.6, 2, 2.6, 3, 3.6 and 4. The first model called the baseline model captures the progression of the disease through the population without any intervention. This is aimed at revealing the dynamics of the pandemic in the absence of mitigation. The second model called the baseline with social distancing model incorporates a social distancing scheme where agents limit their regular pattern of contact by 50% as a preventive measure. This is aimed at creating an alternate view for examining how social distancing alone impacts disease spread.

The third and fourth models are the main cases of interest in this thesis. Here the impact of agents attitudes and resolutions towards the recommended protective measures implemented in the model are evaluated. For this experiment, the models are configured in the Complete Information Mode so all agents are informed ab initio and can make those

choices.

In the case of the third model, the agent population is configured such that negative attitudes dominate the population. The attitude configuration was set as: positive - 15%, negative - 65%, and neutral - 10%, hence is called the largely negative model. It is configured to approximate the behavior dynamics of the current U.S. population. For the fourth model, the agent population was configured with dominant positive attitudes geared towards the dynamics of a population that is more inclined to accept the health recommendations. The attitudes were set as: positive - 75%, negative - 15%, and neutral - 10%, and is thus called the largely positive model. 30 million agents were vaccinated on day 30 in both cases as part of the protective scheme.

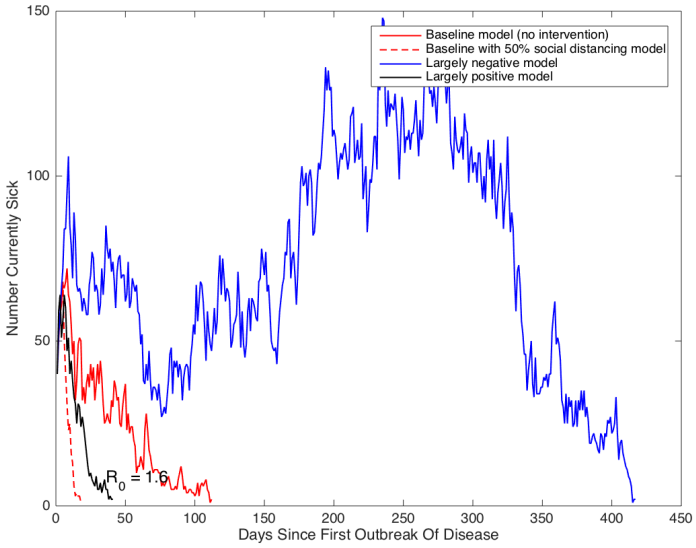
The summary results obtained from the models are recorded in Tables 2, 3, 4, 5, 6 and 7. The 'Duration' column shows the simulation time measured in days. The 'Number Currently Sick' column captures the maximum number of agents that got sick (i.e., maximum current incidence) during the simulation and the specific day or days it occurred. This number is also expressed as a percentage of the total population and is recorded under the '%' column. The corresponding means and standard deviations are also recorded. The 'Total Infected' column captures the disease burden expressed as a sum (Total) and a percentage (%).

5.2.1 Simulation for $R_0 = 1.6$

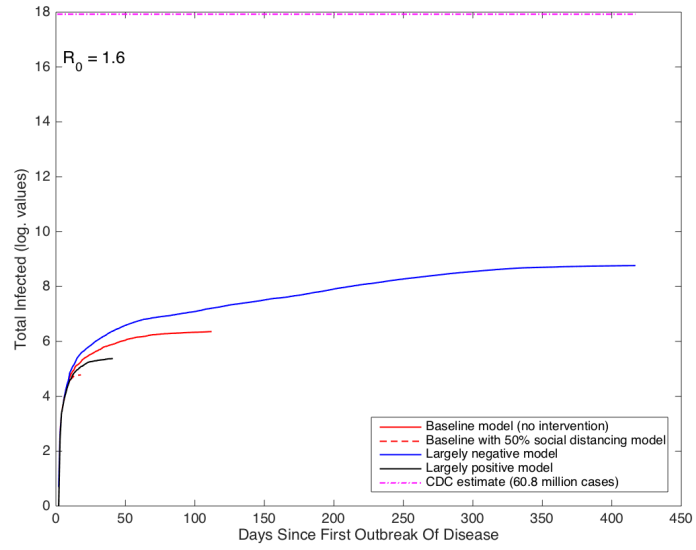
The key results obtained for the simulation at $R_0 = 1.6$ are summarized in Table 2. The plots for the Number Currently Sick (current incidence) as well as the Total Infected (disease burden) are shown in Figure 18. Selected images showing the spread of the disease in the population at selected time periods during the simulation is shown in Figure 19.

Table 2: Summary simulation results for $R_0 = 1.6$

		Number Currently Sick					Total Infected	
	Duration (days)	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	Total	%
Baseline	112	72	2.62×10^{-5}	8	23.99	18.41	576	20.92×10^{-5}
Baseline w/sd	18	68	2.47×10^{-5}	5	27.94	23.48	119	43.23×10^{-6}
Negative config.	417	148	5.38×10^{-5}	235	72.20	34.01	6382	23.18×10^{-4}
Positive config.	41	64	2.33×10^{-5}	3, 6	24.15	20.25	216	78.47×10^{-6}



(a)



(b)

Figure 18: Plots of (a) the Number Currently Sick, and (b) Total Infected for simulation at $R_0 = 1.6$. The disease profile (incidence and burden) of the models indicates that disease has a low infectivity in the population (i.e., endemic) as only less than 6,500 agents (or less than 1% of the population) were affected by the disease in the worst case (the negative model). The other models had a much better performance than the negative model.

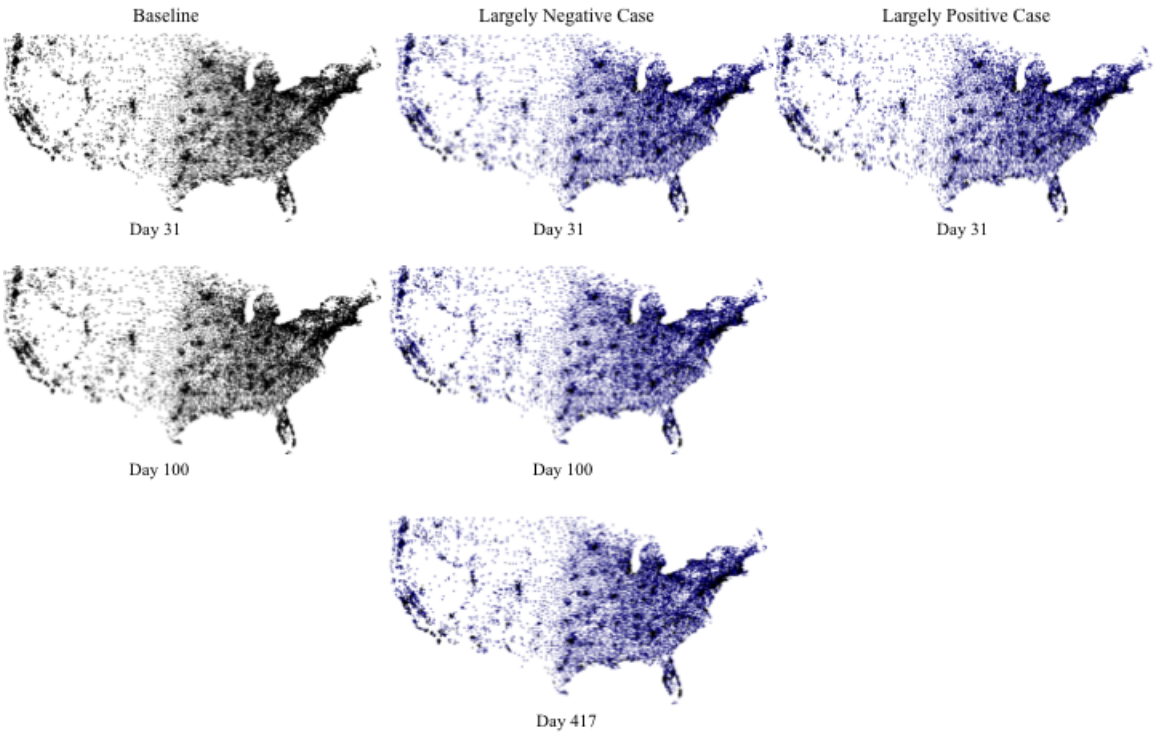


Figure 19: Selected images showing the spread of the disease in the population for the simulation at $R_0 = 1.6$. The images are captured on three days—day 31, 100, and 417 to give a perspective of the spread. The black colored pixels indicate susceptible agents and the blue color shows agents that have recovered from the disease either naturally or by vaccination. The impact of the disease is not visible in this map since only so few got infected. The vaccinated agents (30 million) dominate the blue color in this map since so few got infected and recovered in the first case.

5.2.1.1 *Discussion of results for* $R_0 = 1.6$

The results obtained from this simulation shows that the disease had a low transmissibility or severity (measured by the disease burden) in the population as just less than 1% of the population got infected in the worst case (negative model). In comparison to the other models, the negative model performed worse possibly because of its negative bias that causes agents to largely reject the recommended protective measures. This bias caused the disease to remain longer in the population in comparison to the others. This suggests that the behavior of agents in population can allow the disease to remain longer in the population than preferred even at low-levels of severity. The result of the positive model which captures a more desirable population configuration, suggests that adherence to the recommendations can help quickly contain the outbreak.

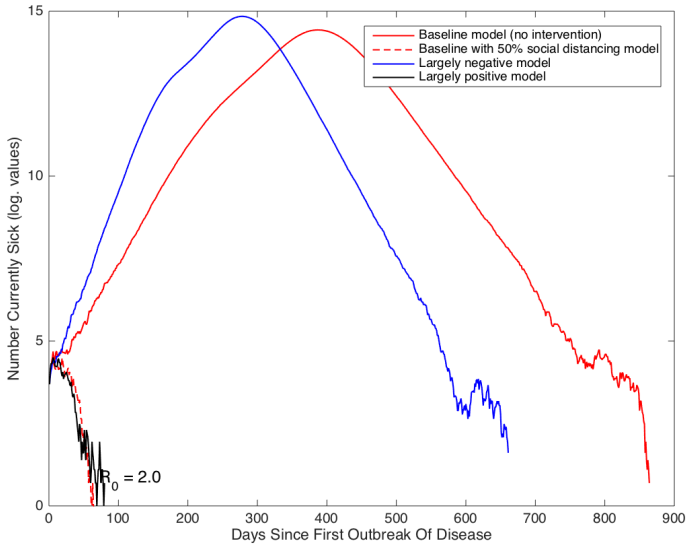
In a sense, the transmissibility of the virus in this case behaves like that of $R_0 \leqslant 1$ for non-spatial homogenous mixing models where a disease dies out in the population quickly. At best, infected agents may 'clump' together but will not be wide-spread uniformly (common to spatial models like MASSAPIS [202]). The disease burden in all of the models were far less than the CDC estimate (60.8 million cases).

5.2.2 Simulation for $R_0 = 2$

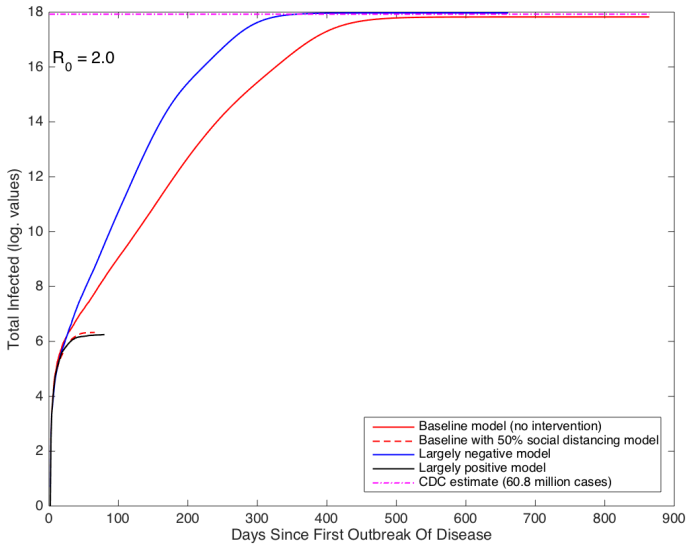
The key results obtained for the simulation at $R_0 = 2$ are summarized in Table 3. The simulation plots are shown in Figure 20 and selected images showing the spread of the disease at selected time steps during the simulations are shown in Figure 21.

Table 3: Summary simulation results for $R_0 = 2$

		Number Currently Sick					Total Infected	
	Duration (days)	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	Total	%
Baseline	864	1,849,839	0.67	387	299289.63	522280.62	54,973,536	19.97
Baseline w/sd	64	90	3.27×10^{-5}	19	39.43	28.16	119	20.34×10^{-5}
Negative config.	661	2,790,057	1.01	278	453005.55	783012.25	63,654,365	23.12
Positive config.	80	90	3.27×10^{-5}	6	29.90	29.13	517	18.78×10^{-5}



(a)



(b)

Figure 20: Plots of (a) the Number Currently Sick, and (b) Total Infected for simulation at $R_0 = 2$. Note that the logarithm value is used for the plots here because of the wide variation in result data. Two contrasting results are revealed here—the baseline and negative models exhibit epidemic characteristics (about 20% of the population affected) and approximate the CDC estimate of 60.8 million individuals affected, while the baseline with social distancing and positive models exhibit endemic characteristics (less than 1% of the population affected).

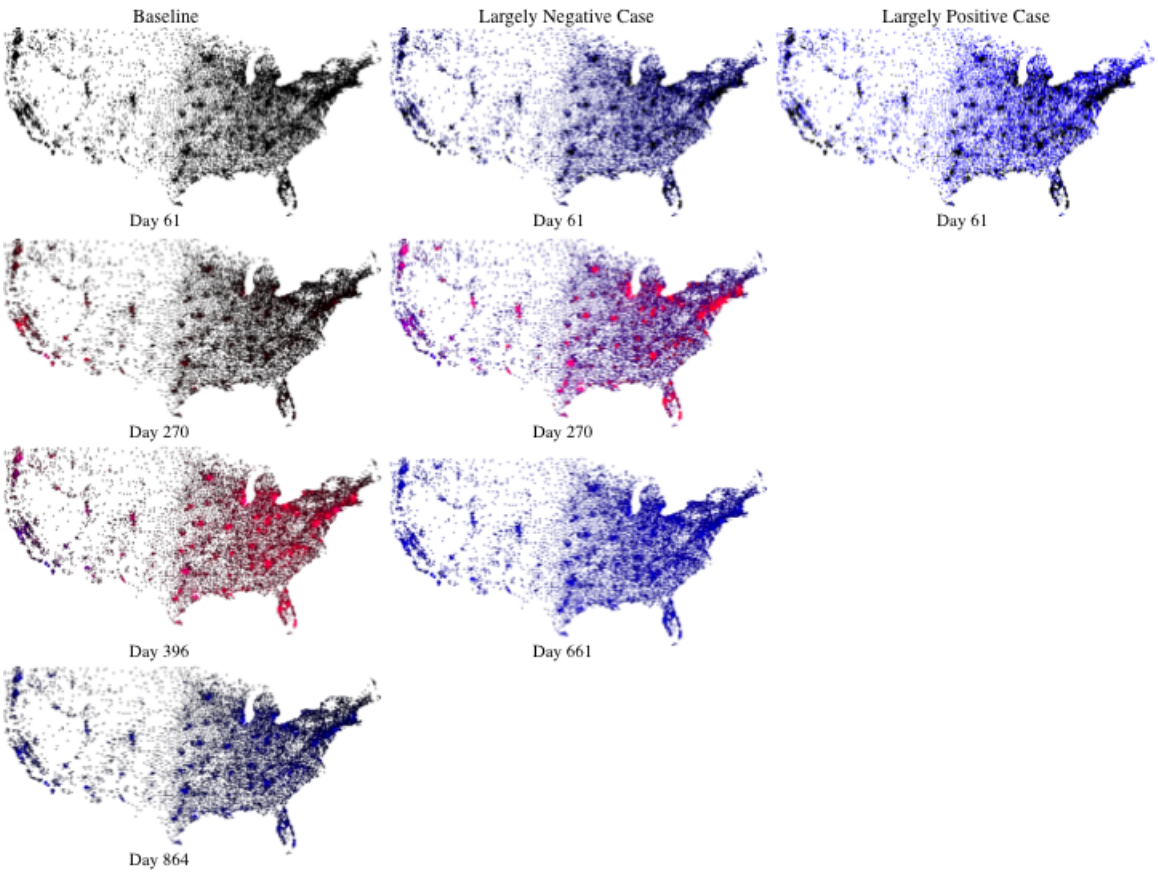


Figure 21: Selected images showing the spread of the disease in the population for simulation at $R_0 = 2$. The images are captured on four randomly selected days—day 60, 270, 661, and 864. The same color code adopted in the previous map is used here. The infection activity can be seen in the baseline and negative models, unlike in the positive model. The disease spread was faster in the negative model than the baseline but ended about 200 days before the baseline. The positive model contained the disease in about two months.

5.2.2.1 Discussion of results for $R_0 = 2$

Two noticeable sets of results are obtained for this scenario. First, the spread of the disease in the baseline and negative models show epidemic spread properties and both models have a disease impact that closely approximate the CDC estimate observed during the 2009 pandemic (disease burden of 55 million and 64 million respectively compared to CDC's 60.8 million affected). This suggests that the R_0 of the outbreak using this framework is closer

to 2 than 1.6 which is in the range of CDC's estimate of $1.3 - -2.3$ [257]. This approximation thus functions like a form of 'validation' of the negative model, hence the framework, albeit in a weak sense. Second, the disease was contained in both the baseline with social distance and positive models within three months of the outbreak without reaching epidemic proportions (the peak incidence rates and disease burdens for these models were insignificant as shown in Table 3). This suggests that the interventions adequately contained the disease as desired. More so, it showed that the positive model which represents a population more inclined to accepting protective recommendations effectively contained the disease with minimal disease impact (less than 600 agents affected). Thus, there is a clear incentive for the government to drive initiatives that motivate or inspire its citizens to be positively inclined to believe government issued health recommendations.

Although the widely referenced CDC estimate used as the ground truth data for validation here only measured a disease activity period of one year, April 2009 - April 2010 [257]. In essence, the CDC data only points to the fact that the epidemic period was within this one year window of activity. In this simulation scenario, by the one year mark, the disease burden of the negative model had practically peaked (at 61.6 million individuals infected in comparison to CDC's 60.8 million), while the baseline model was about half-way (18.9 million individuals infected) to its peak value (see Figure 20b). So the results of the negative model which is configured to the behaviors (attitudes and resolutions) of the current modeled population fairly approximates the CDC total estimate. The baseline model eventually achieves this close result towards the end of the simulation. At their peaks, the illness attack rates[3] for the baseline and negative models are approximately 0.7% and 1% respectively, indicative of the seriousness of the epidemic [114].

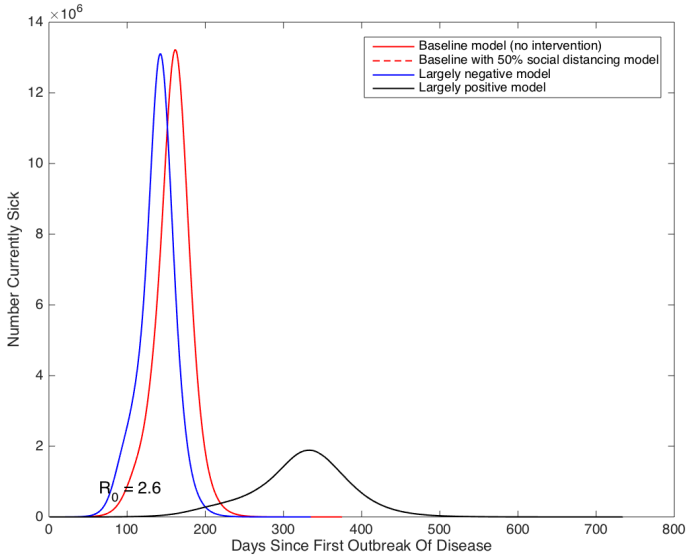
5.2.3 Simulation for $R_0 = 2.6$

The key results obtained for the simulation at $R_0 = 2.6$ are summarized in Table 4. The simulation plots are shown in Figure 22 and selected images showing the spread of the disease at selected time steps during the simulations are shown in Figure 23.

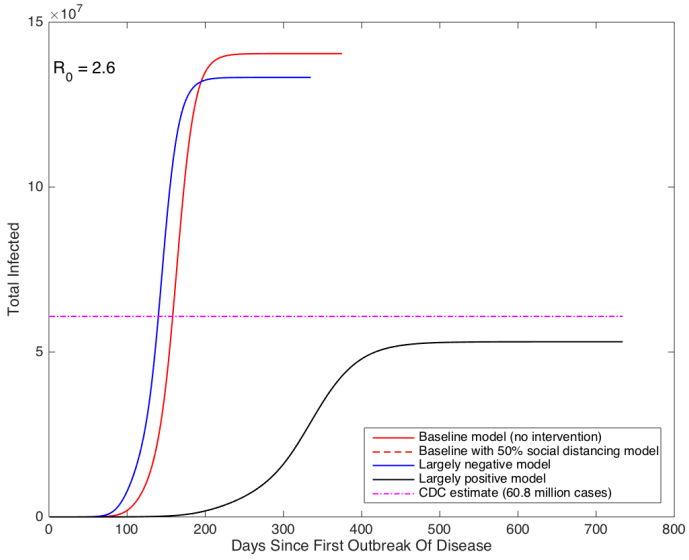
[3]Defined as the number of new cases divided by the total population.

Table 4: Summary simulation results for $R_0 = 2.6$

		Number Currently Sick					Total Infected	
	Duration (days)	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	N	%
Baseline	375	13,217,168	4.80	162	1762087.19	3454857.36	140,461,310	51.03
Baseline w/sd	66	90	3.27 x 10^{-5}	19	39.42	28.16	560	20.34 x 10^{-5}
Negative config.	335	13,102,777	4.76	143	1870842.85	3471075.74	133,233,718	48.40
Positive config.	734	1,887,405	0.69	333	40346.01	543781.82	53,104,660	19.29



(a)



(b)

Figure 22: Plots of (a) the Number Currently Sick, and (b) the Total Infected for simulation at $R_0 = 2.6$. The disease is severe in both the baseline and negative models as shown by the high incidence rates and disease burdens that more than doubles the CDC estimate.

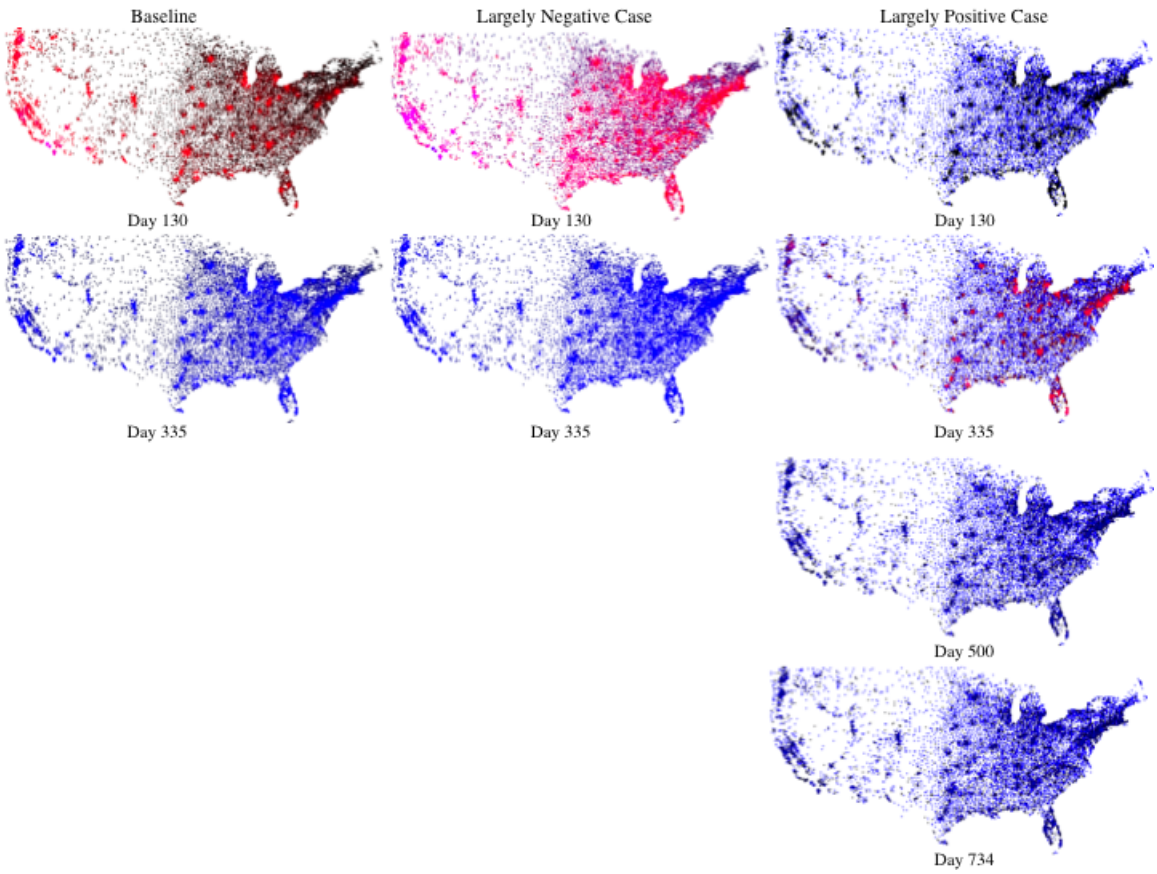


Figure 23: Selected images showing the spread of the disease in the population for simulation at $R_0 = 2.6$. The images capture the spread of the disease in the population on four randomly selected days—day 130, 335, 500, and 734. The baseline and largely negative model have closely related patterns because they have similar illness attack rates and disease burdens (see Table 4). However, the positive model also developed into an epidemic after about a year (see day 335 image) out of its roughly two-year duration period. The epidemic peaked period lasted for about three months before the disease receded in this case.

5.2.3.1 Discussion of results for $R_0 = 2.6$

Three features are highlighted in the results from this simulation. First, the baseline and negative models exhibit characteristics of a serious pandemic with illness attack rates of about 5% indicative of the severity of the disease since this is more than the 1% attack rate suggested by [114]. Also, about 50% of the total population became infected over the course of the simulation (see Table 4). Second, the positive model which represents

a more desirable target population (i.e., in terms of favorable attitudes and resolutions) also reached epidemic proportions that affected almost 20% of the population over its two year simulation period. This closely approximated the CDC estimate, so at this scenario, the interventions provided by the positive model is unable to prevent the disease becoming an epidemic. Only the baseline with social distancing model contained the spread of the disease with good results (within 90 days and less than 600 agents infected).

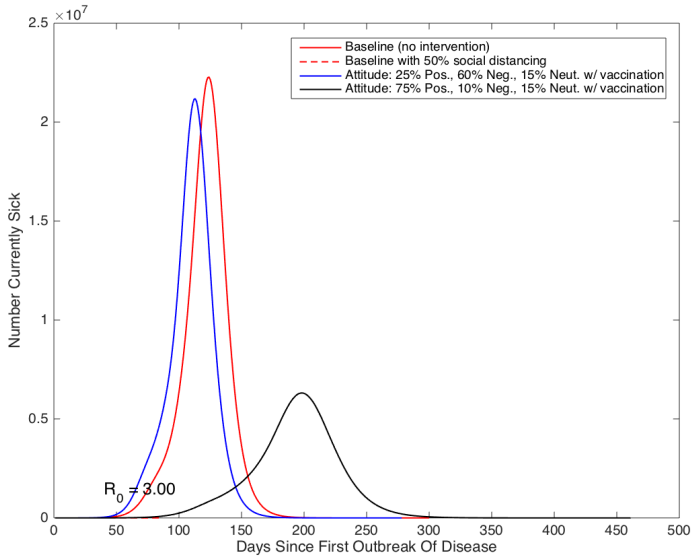
A closer observation of the results from the positive model showed that the disease appeared initially contained within the first year (300 days) of the disease (see Figure 23a), but then the incidence rate rose during the next 75 days transforming it into an epidemic with a result close to the CDC estimate (i.e., approximately 53 million affected in the positive model compared to CDC's estimate of approximately 61 million affected individuals). This presents an opportunity to apply more policy interventions methods within the first year of an outbreak to further curtail the spread of the disease if this model configuration is adopted as the target population. The results of the baseline with social distancing model lends support to this as it showed that limiting agents contact can contain the disease at this scenario.

5.2.4 Simulation for $R_0 = 3$

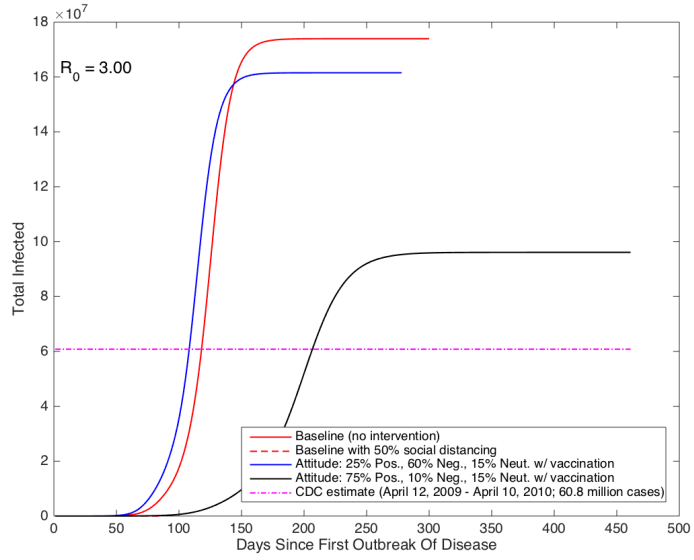
The key results for the simulation at $R_0 = 3$ is summarized in Table 5. Figure 24 shows the simulation plots of the results and images showing the spread of the disease at selected time steps are showing in Figure 25.

Table 5: Summary simulation results for $R_0 = 3$

		Number Currently Sick					Total Infected	
	Duration	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	N	%
Baseline	300	22,277,209	8.09	124	2727405.28	5613491.74	173,937,468	63.19
Baseline w/sd	86	100	3.63×10^{-5}	22, 23	48.30	31.13	879	31.93×10^{-5}
Negative config.	278	21,183,784	7.70	113	2733224.88	5401129.15	161,522,667	58.68
Positive config.	461	6,314,208	2.29	198	980584.36	1733611.83	96,095,848	34.91



(a)



(b)

Figure 24: Plots of (a) the Number Currently Sick, and (b) Total Infected for simulation at $R_0 = 3$. At this scenario, the disease is a severe pandemic in the case of the baseline and negative models. The disease burdens in both models affected more than half the population in both cases indicative of its severity (58% and 63% of the population respectively). The impact of the disease in the positive model was also significant as it affected up to 35% of the population (exceeding CDC's estimate which affected about 20% of the population).

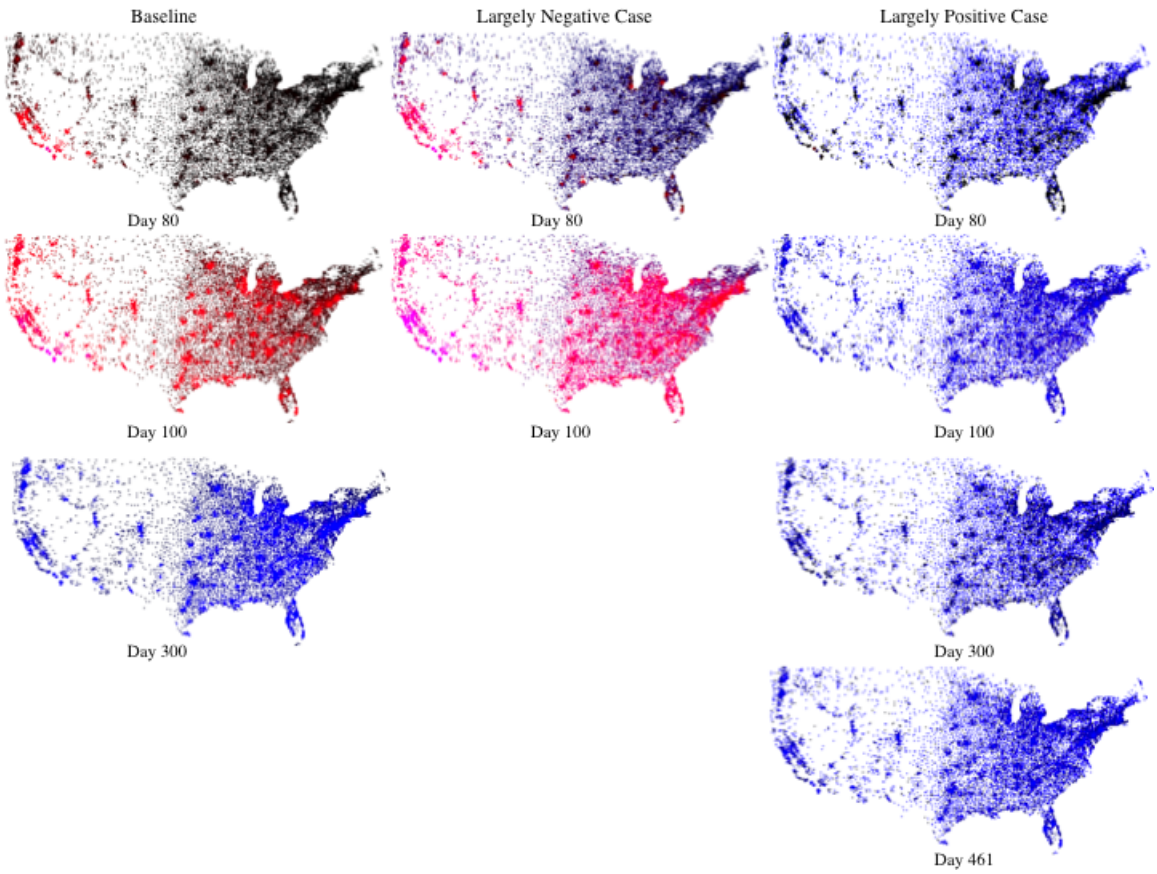


Figure 25: Selected images showing the spread of the disease in the population at $R_0 = 3$. The images capture the spread of the disease in the population on four randomly selected days—day 80, 100, 300, and 461. Because of the similarity in the model results of the baseline and negative models, the spread patterns also look alike but offset by a few days. However, the infection is not visually obvious in the case of the positive model at the time steps selected here.

5.2.4.1 Discussion of results for $R_0 = 3$

At this scenario, the pandemic is quite severe affecting more than half of the population in both the baseline and negative models (about 63% and 59% of the population respectively). The pandemic was also significant in the case of the positive model (affecting about 35% of the population) indicative that the target population as constituted (by attitudes and resolutions) would not be able to contain the disease. The disease was however contained in the baseline with social distancing model which suggests that in the case of the target

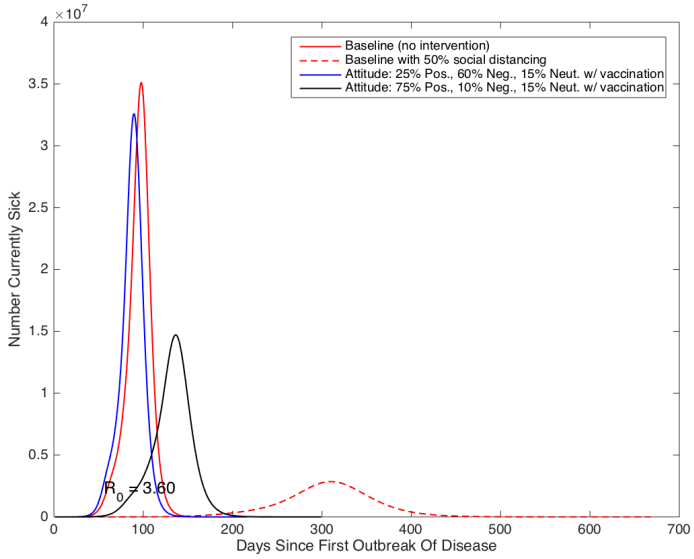
population (the positive model), additional policy measures are needed in addition to the favorable attitudes and resolutions of the population.

5.2.5 Simulation for $R_0 = 3.6$

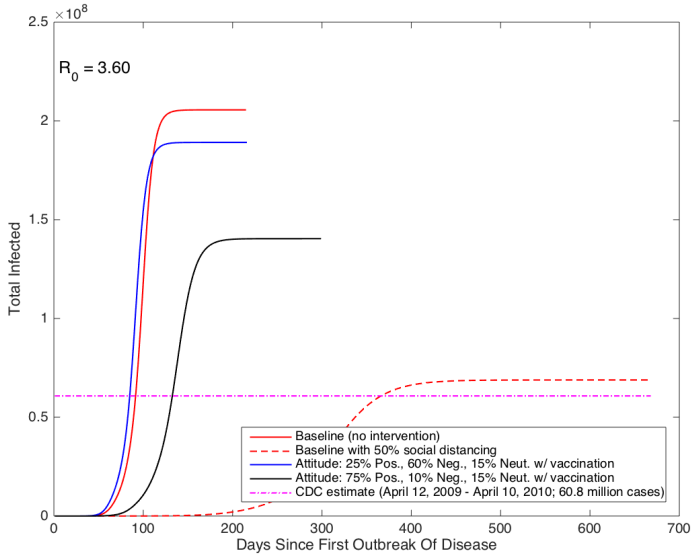
The key results for the simulation at $R_0 = 3.6$ are summarized in Table 6. The simulation plots for the current incidence and disease burden are shown in Figure 26 and images showing the spread of the disease at selected time steps are shown in Figure 27.

Table 6: Summary simulation results for $R_0 = 3.6$

		Number Currently Sick					Total Infected	
	Duration	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	N	%
Baseline	215	35,135,908	12.76	98	4497712.21	8967534.90	205,566,117	74.68
Baseline w/sd	668	2,852,286	1.04	310	485015.99	817828.98	68,869,972	25.02
Negative config.	216	32,599,689	11.84	90	4118200.73	8305350.80	189,093,045	68.69
Positive config.	299	14,719,213	5.35	136	2208724.91	3970540.04	140,381,322	60.00



(a)



(b)

Figure 26: Plots of the simulation results for $R_0 = 3.6$. Plots of (a) the Number Currently Sick and (b) the Total Infected for the simulation at $R_0 = 3.6$. At this scenario the disease resulted in a pandemic in all the models simulated (exceeding the CDC estimate). The baseline and negative models both have a significant spike in the incidence rate (with over 30 million agents infected at in just one day).

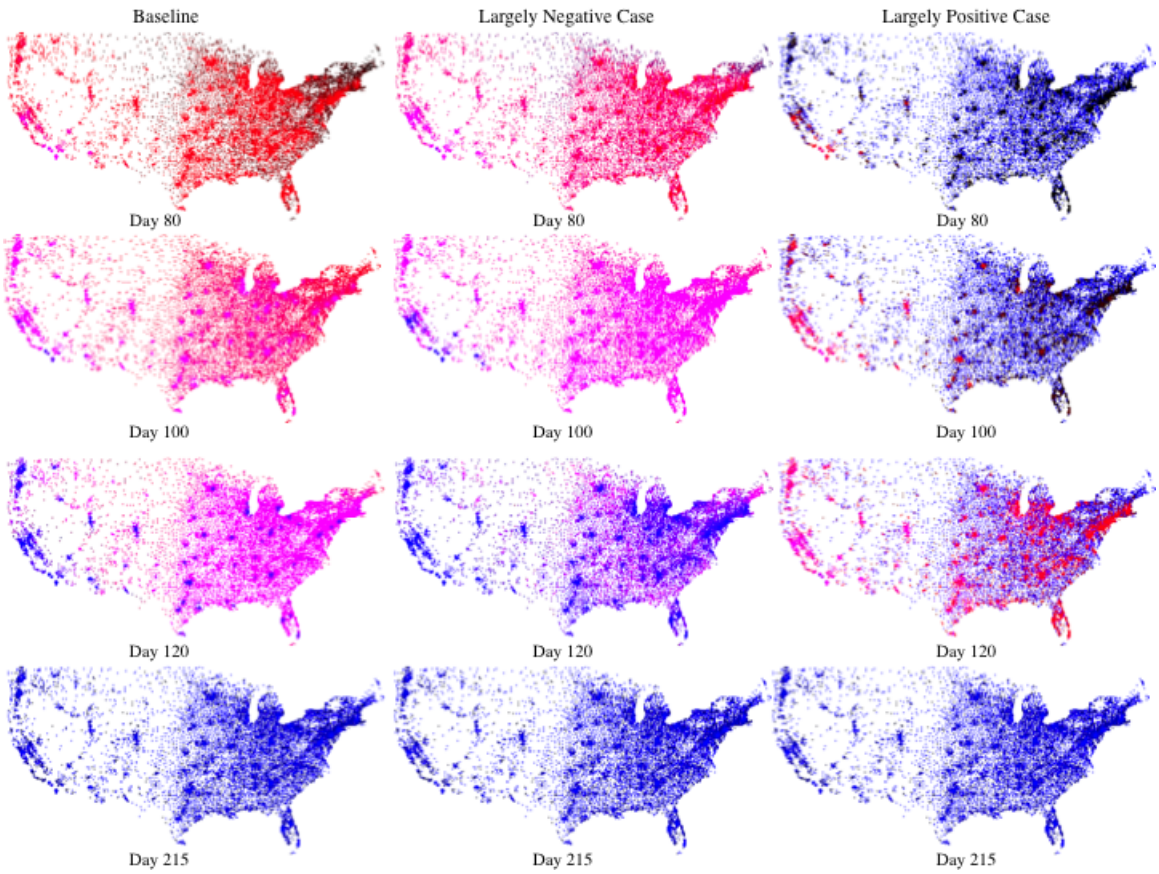


Figure 27: Selected images showing the spread of the disease in the population at $R_0 = 3.6$. The images capture the spread of the disease in the population on four randomly selected days—day 80, 100, 300, and 461. The infection is very severe and very wide-spread in the population within 100 days in both the baseline and largely negative models. By day 215, the infection was mostly over in all the models except the baseline with social distancing model (not shown here).

5.2.5.1 Discussion of results for $R_0 = 3.6$

At this scenario, the disease resulted in a pandemic in all the models tested. In the baseline and negative model, the disease manifested as a very severe pandemic with attack rates greater than 10% and affecting a significant portion of the population in both models (75% and 69% of the population respectively). The disease is also severe in the positive model affecting 60% of the population. Even for the baseline with social distancing model where the probability of contact is reduced by half, 25% of the population was still affected by

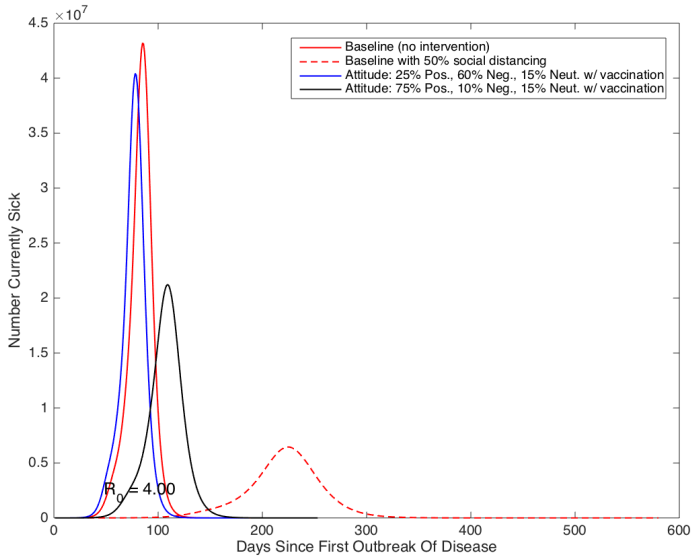
the disease. This suggests that attitudes alone are not sufficient to contain and mitigate the disease at this scenario. The virus is quite virulent here so a combination of strategies would be needed to mitigate and contain it. This is consistent with what other researchers have noted—that a combination of mitigation and containment strategies such as the use of antivirals (used as a prophylactic and/or therapeutic drug), vaccination (for example, targeted vaccination), and social distancing (even including personal hygiene) are needed to effectively contain a highly virulent strain of pandemic influenza virus [100, 101, 181, 303, 293].

5.2.6 Simulation for $R_0 = 4$

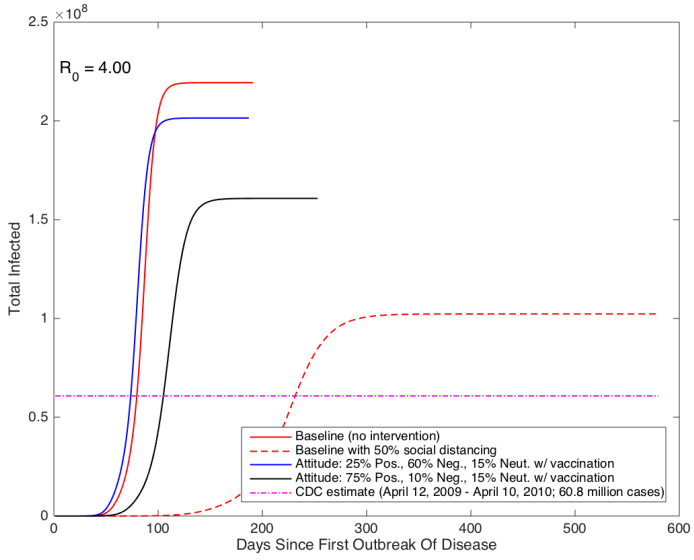
The key results for this scenario is summarized in Table 7. The simulation plots showing the current incidence and disease burden are shown in Figure 28 and selected images showing the spread of the disease at specific time steps during the simulation are shown in Figure 29.

Table 7: Summary simulation results for $R_0 = 4$

		Number Currently Sick					Total Infected	
	Duration	N (Max)	%	Day(s) occurred	Mean	Std. Dev.	N	%
Baseline	191	43,190,451	15.69	85	5402050.47	10970917.50	219,343,798	79.68
Baseline w/sd	580	6,450,647	2.34	225	829549.99	1660018.13	102,278,474	37.15
Negative config.	187	40,430,006	14.69	78	5067307.66	10246295.19	201,444,997	73.18
Positive config.	253	21,218,180	7.71	109	2989243.09	5667105.19	160,766,002	58.40



(a)



(b)

Figure 28: Plots of (a) the Number Currently Sick, and (b) the Total Infected, for the simulation at $R_0 = 4$. The disease is very severe at this scenario for all the models affecting up to 80% of the population in the worst case (the baseline model) and over one-third (37%) of the population in the best case (baseline with social distancing). The disease circulated for a shorter duration (less than a year) in all the models except the baseline with social distancing model.

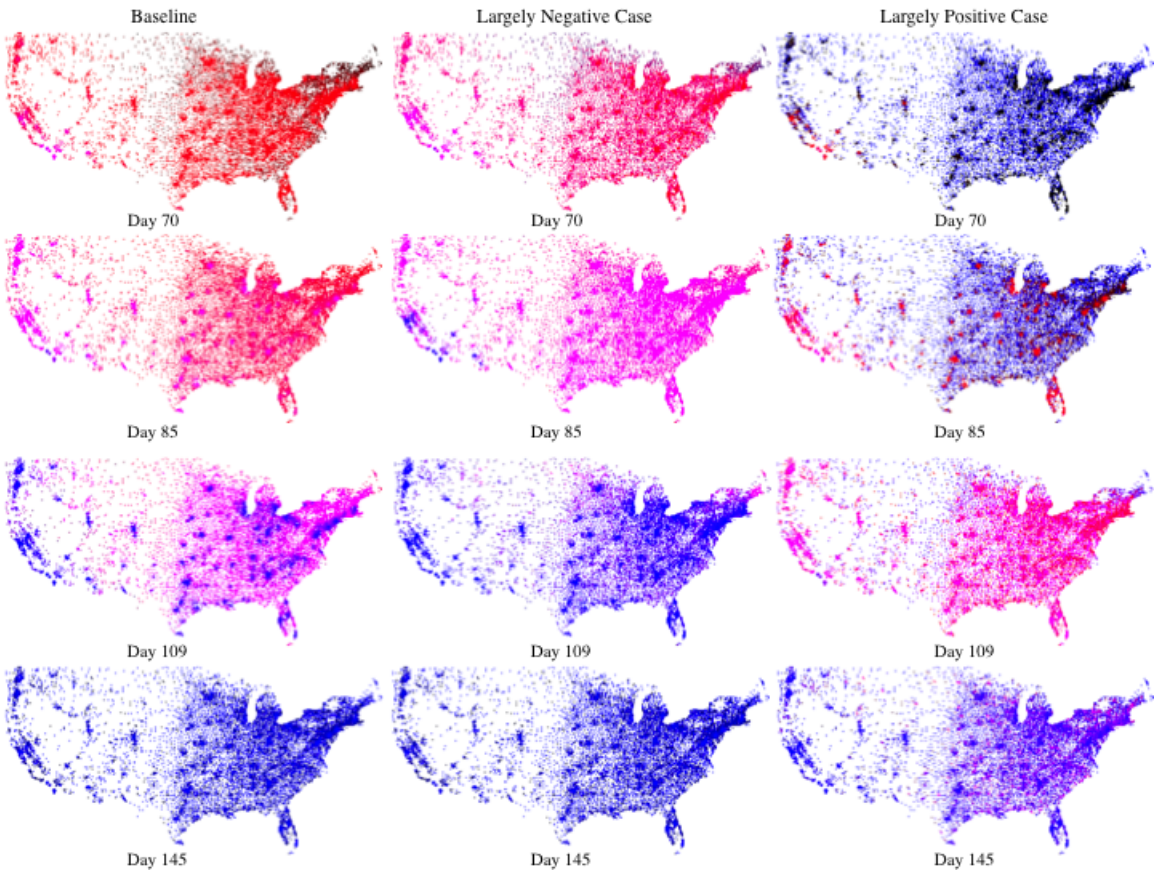


Figure 29: Selected images showing the spread of the disease in the population at $R_0 = 4$. The images capture the spread of the disease in the population on four randomly selected days—day 70, 85, 109, and 145. The virulence of the virus can be seen by the intensity of the map and the day of occurrence (earlier than the previous scenarios).

5.2.6.1 Discussion of results for $R_0 = 4$

For this case, the disease was much more severe than the previous scenarios. Here it affected almost the entire population of agents in the baseline and negative models—80% of the population or 219 million agents in the baseline and 73% of the population or 201 million agents in the negative model. The severity of the disease is further underscored by its short duration or period of circulation in the population. Its virulence can be seen in Figure 28 where the disease affected over 40 million people in one day at its peak (day 85 and 78 in the baseline and negative models). This is about 15% of the population infected in just one day in both models. The disease was also virulent in the positive model where it

infected more than 7% of the population in just one day and more than half the population (58% or 160 million agents) over its course of duration. It also had a similar effect in the baseline with social distancing model where it infected 2% of the population in one day (at its peak) and more than one-third of the population (37% or 102 million agents) over the duration of the simulation.

The results of this simulation suggest that the current recommendations and target population configuration (as set in the positive model) are insufficient to curtail the spread of the disease. Even the model where all contact is limited by 50% was also inadequate. This suggests the need of more strategies to contain the disease outbreak, possibly a combination of strategies as noted in the previous discussion (Section 5.2.5.1).

5.3 Discussion of Simulations

The models simulated for this study were chosen to include only the most basic features essential for investigating the spatial patterns of pandemic influenza spread in the U.S. population. I have omitted many features and made considerable approximations in the features included. Hence, it is appropriate to discuss some of the shortcomings of the models before interpreting the results.

As previously noted, Influenza outbreaks typically occur in multiple outbreaks or successive "waves[4]" [179, 266, 200, 131], and vary greatly in severity during the outbreaks [140, 176]. However, the mechanism responsible for the multiple waves of infection is uncertain [207]. Recent pandemic influenza history shows that the infection spreads mostly in two waves—a mild first wave followed by a severe second wave [266, 200, 131]. This was the case during the 2009 H1N1 outbreak[5] in the U.S. The infection came in two waves—June and late October 2009 with the latter the deadlier [142]. So this means that the incidence curve for the actual data will show a two-wave profile.

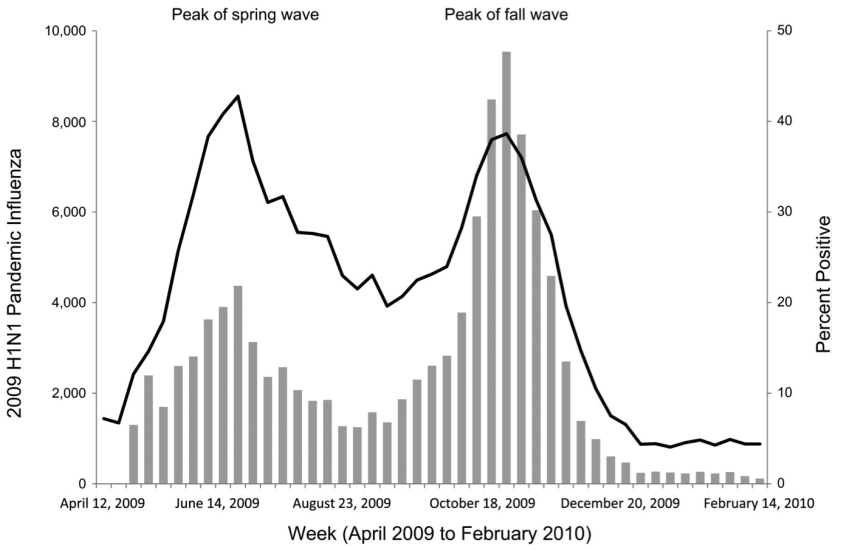
Despite the multiple-wave nature of the outbreak of the disease, most of the infection

[4]Three waves of incidence and mortality were seen in the 1918 influenza pandemic in London, England [132].

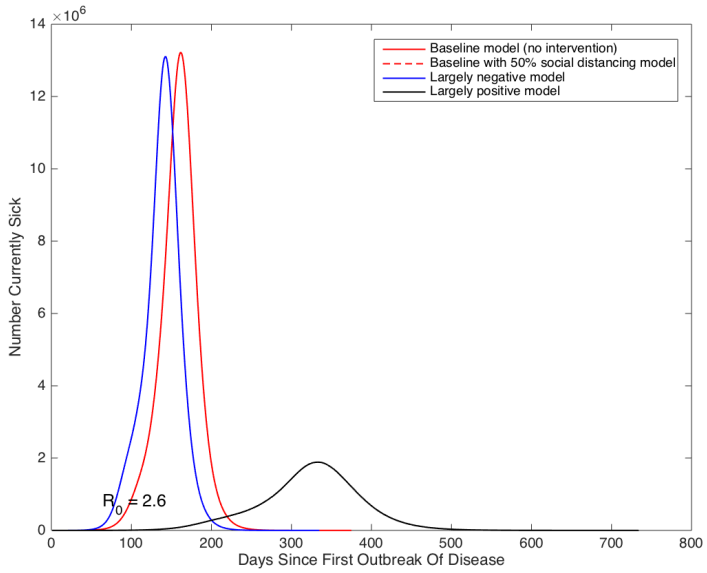
[5]Merler et al. note that while the pandemic occurred in two waves in the U.K. (a first wave in early summer and a second wave in autumn), the rest of Europe experienced a single wave (in autumn/winter) [194].

(in terms of morbidity and mortality) is often attributed to just one of the outbreak waves, thus, modelers often approximate the epidemic curve with one wave for model simplicity [186, 133, 187]. For example, scholars such as [114, 179, 125, 13] assumed[6] a single-wave epidemic curve in their works. I followed this same approach in this study and assumed the epidemic curve of the outbreak modeled follows a single-wave pattern. However, this assumption may have implications for the actual pattern of spread of the disease and may lead to different results and conclusions (as measured by the disease burden). The general belief is that this difference in model results (between a single-wave and multiple-wave epidemic curve pattern) is often insignificant and within acceptable limits of the morbidity and mortality rates of most influenza outbreaks. A visual comparison of a single-wave and double-wave epidemic curves is shown in Figure 30 to aid understanding.

[6]Their bases for this assumption may vary. For example, Longini et al. [179] explored the most effective strategies for the use of antiviral drugs to contain the disease at the onset of the first wave thus avoiding the second wave when effectively contained.



(a)



(b)

Figure 30: Visual comparison of incidence curves of the 2009 outbreak for the actual and simulated data to highlight the double-waved and single-waved nature of a disease outbreak. Figure (a) is the incidence curve for the actual transmission (Figure source: [142, p. S14]), and (b) is the incidence curve for the simulated scenario using $R_0 = 2.6$.

Another concern is the use of the basic infectiousness number, R_0, as a good measure of disease transmissibility. First, estimating a value for R_0 is challenging as it is a complex

measurement to make and thus the estimation in practice is often near arbitrary and not precise [186, 134, 290]. Infection transmissibility is a heterogeneous, complex, and dynamic phenomenon that depends on factors such as pathogenic genetic diversity, host biology, the environment, heterogeneity in human contact networks, and behavior. For example, different levels of transmissibility are known to occur in different households and communities during pandemic influenza outbreaks [180, 52, 50]. Also, secondary attacks of the virus exist and contribute significantly to the transmissibility of the disease [180, 125]. Second, R_0 is not constant throughout the population [282, 186, 134]. However, here as in other similar studies [114, 179, 52], R_0 is assumed to be constant throughout the population and for the duration of the simulation for model simplicity reasons.

The vaccination approach employed in this work also has a number of concerns. Typically, the vaccine deployed during a pandemic outbreak is delivered in doses and staged (i.e., applied in phases targeted first to those deemed at greatest risk, for example, to school-aged children and the elderly [181, 303]). This is because of the delay in manufacturing homologous-matched vaccines to provide immunity to the novel virus (this gives rise to the supply and distribution issues). It is therefore quite difficult to deploy vaccines to a very large portion of the population in a single day as assumed in this thesis (30 million individual agents vaccinated on day 30). This may impact the population differently if a staged approach were employed.

In terms of the vaccination coverage, 10% of the agent population was vaccinated in MASSAPIS to approximate the low vaccination coverage[7] which occurred during the 2009 outbreak. However, vaccinating just 10% of the population universally without any strategy or target is not recommended to achieve good results [100, 101, 181, 303]. Rather a higher coverage is suggested. For example, Yang et al. [303] suggest strategies with a coverage of up to 50% for $R_0 < 1.6$ and 70% otherwise to obtain a better mitigating effect.

A lot of assumptions are also made by modelers because of the challenges of incorporating the dynamics of human behavior in infectious disease models [89, 98, 107]. In this

[7]For the 2009 outbreak, vaccine coverage varied widely among subpopulations and less than 10% of the population was vaccinated [36].

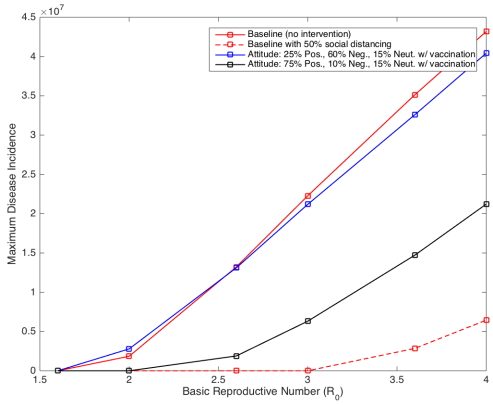
thesis, the attitudes and resolutions developed are simplifications of very complex processes and may not adequately represent human motivation and behavior. However, since there is a need to capture more of human behavior into disease models, a simple approximation like this is needed as a first step in developing more complex models.

Finally, the assumptions regarding the contact pattern is one of the key determinants of the outcome of population models like this because the contact pattern plays a vital role in shaping disease outcomes [233, 277, 193]. Unfortunately, a lot is still unknown about how different levels of population heterogeneity and patterns of human mobility affect the progression of pandemic influenza during an outbreak. Since disease incidence tend to occur in spatial clusters during the initial stages of an outbreak, how agents form clusters in the model can highly influence the spread of disease. The distribution and movement of people (which is strongly driven by the population density) acts as a strong determinant of the spread. As a result, census-derived movements patterns are commonly used to describe population density in models [235]. MASSAPIS incorporates the census-driven movement patterns used to describe the contact itinerary of agents in GSAM. The contact patterns in the model can be considered as reasonably good approximations.

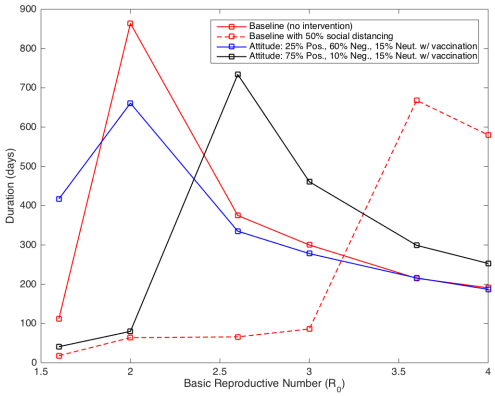
5.3.1 Summary of the Key Results

A summary plot of the key results obtained from the simulations is presented in Figure 31. As the disease transmissibility R_0 is increased, the number of those currently sick (current incidence) and total infected (disease burden) increases while the duration declines. This result is not surprising and is consistent with what others have reported [100, 101, 181, 303]. Essentially, as the virulence of a virus increases, the faster it will circulate through a population, the shorter the duration will be, and a greater number of people it will affect.

The impact of this transmissibility on the duration of the disease is not easy to interpret because of the evolutionary nature of agent-based models (see Figure 31b). The results from this study suggest that the virus in the baseline and negative models initially circulated for a relatively longer time period than the positive model until the disease got severe ($R_0 \geqslant 2.0$). Afterwards, the virus in the positive model circulated for a longer period than the baseline



(a)



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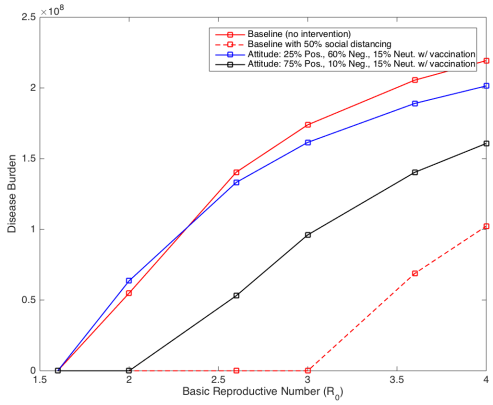

(c)

Figure 31: Summary of the overall key results obtained for each simulation. Summary plot of (a) the day with the highest disease incidence, (b) duration of the disease, and (c) the disease burden (total infected) for the six simulations.

and negative models. However, as the virulence increased, the duration of the simulations in the baseline, negative, and positive models appear to converge towards the same value. This suggests that the structural advantages embedded in the positive model by construction (i.e., the favorable attitude and resolutions) erode as the level of the severity of the virus increases. The result of the baseline with social distancing model appears to follow the same pattern.

So the advantages of the positive model (where the population is more inclined to adopt the protective recommendations) diminish as the severity of the disease increases. By $R_0 = 3$, almost 35% of the population (100 million agents) was affected by the virus compared to about 20% (53 million agents) at $R_0 = 2.6$. It may be possible to obtain an improvement in this result by increasing the configuration of attitudes in the model to be more positive. For instance, increasing the positive attitude from 75% to a value closer to 100% to represent a population with a more highly positive attitude demographic. However, this will not be sufficient to contain a very severe form of the disease. The results of the baseline model with social distancing suggests that limiting contact alone will also not suffice to contain the disease at high levels of severity. Rather a policy that involves a combination of strategies would be needed to contain the disease at this level [100, 101, 181, 303, 293]. For example, implementing a combination of strategies such as a more targeted vaccination scheme (the most at risk of infection) along with vaccinating more agents in the population (increasing vaccination rates to at least 50% of the population may give better results). Implementing an improved social distancing scheme along with targeted vaccination and an improved attitude configuration will help to mitigate and control a disease at very high levels of severity.

It should be noted that the impact of the disease transmissibility on the simulation results is not entirely easy to extrapolate because of the evolutionary nature of agent-based models. Because agent-based models are generative models [86], extrapolating the impact of one factor on one of the outcomes is not straightforward. For example, reducing the contact rate by one-half as was done in the baseline model with social distancing model does not necessarily translate into a corresponding reduction in disease incidence and burden.

Similarly, doubling R_0 from say 2 to 4 does not directly translate to a doubling of disease incidence or burden.

5.4 Summary

In this Chapter, the results of the simulations obtained from MASSAPIS was presented, the validation method employed described, and a discussion of the results given.

To evaluate the potential for mitigating and controlling an outbreak of pandemic influenza A/H1N1 by varying the attitudes and resolutions of agents in the U.S. population, four models were simulated at six scenarios of disease transmissibility using R_0 values of $1.6, 2, 2.6, 3, 3.6$ and 4. The four models where configured to represent different behavioral approximations of the population. The baseline model represented a population without any intervention, the baseline with social distancing model represented a population with contact reduced by 50%, the negative model represented current behavior in the population, and the positive model represented the target population with more improved behaviors (attitudes and resolutions) and thus better inclined to adopting preventive health recommendations during an outbreak.

The results indicate that while improving the attitudes and resolutions of the population from a largely negative to a positive position improved mitigation and containment strategies, the benefits of this intervention begin to diminish as the severity of the disease increases. And after a certain point, a combination of strategies that includes improved vaccination uptake and social distancing is needed to curtail the spread of the disease.

CHAPTER VI

CONCLUSIONS

6.1 Summary

The goals of this dissertation have been to investigate how changes in human behavior impact the spread of pandemic influenza spread in the U.S. using an agent-based computational model suitable for analyzing the spatial spread of the disease. The objectives include:

1. To develop a computational framework that can model aspects of spontaneous human behaviors for infectious disease analysis. Specifically, the attitudes and resolutions of individuals in a population towards government-issued advisory information during the outbreak;

2. To research how the transmissibility of the influenza virus affects disease incidence and burden during an outbreak.

Results of the first objective include the design and implementation of MASSAPIS, a computational framework capable of modeling human behavior for pandemic influenza spread analysis. MASSAPIS builds upon and extends the GSAM platform developed by Parker and Epstein [219]. MASSAPIS is written in Java and is designed in a modular form to encourage future extensions.

MASSAPIS adopts a multi-agent based simulation paradigm where individuals in the population are represented as virtual agents. The agent population is based on the 2010 U.S. Census data. Social behavior is simulated using each agent's pre-defined itinerary based on any of the following: family, work, or random itinerary events. It is this itinerary movement that determines the probability of agent-to-agent contact that drives disease transmission in the model. The distinctive feature of MASSAPIS is the endowment of agents in the model with attitudes and resolutions towards adopting advisory information

disseminated by the government during the outbreak and the impact it has on the spread of the disease. Two main preventive behaviors are currently built into MASSAPIS—social distancing and vaccination; three attitude attributes—positive, negative, or neutral; and three types of resolutions—inclined, opposed, and indifferent postures towards adopting the recommended preventive behaviors to limit infection. Together, these variables influence an agent's probability of infection and dynamics of the disease spread.

There have been many important models developed to investigate public health questions related to the mitigation and control of pandemic influenza. However, many are not spatial population models that can be used to clearly answer the question posed in this thesis. They lack the incorporation of human behavior changes and how it affects disease prevalence. MASSAPIS represents a modeling paradigm where infectious disease dynamics and behavior are incorporated into the same framework in an interdependent way.

6.2 Future Directions

Incorporation of a more detailed psychological behavior process into MASSAPIS constitutes a potential additional research focus. This dissertation emphasizes the incorporation of attitudes and resolutions as behavior characteristics into behavior-disease models. However, how to endogenize a more detailed behavior decision process into disease models remains an open question. Incorporating more detailed behavior mechanisms in these kinds of models will allow for more accurate representation of the population and thus improved model realism. However, this introduces further computational complexities into the system. So pending the development of cheaper and faster computational resources that can support these kinds of frameworks, simpler approximations will have to suffice.

Exploring ways that social media sentiment can be incorporated into MASSAPIS such that it can capture real-time population-level sentiments is another interesting line of research to explore [146, 59]. Since aggregate sentiments of subpopulations can be fairly easily extracted from social media, they could be used as a better proxy for attitudes in the framework. Already, Twitter has been analyzed as a source for studying behavioral responses to epidemics [161, 162, 241, 258]. For example, vaccination sentiments can be extracted and

matched to resolutions taken to eventually accept or reject the vaccine [40, 244]. Ideally, sentiments would be extracted dynamically and used daily to obtain a more realistic representation of attitudes and resolutions in the population. Disease incidence reports can also be derived from social media and used to update CDC's influenza-like-illness (ILI) activity report, which is used as ground truth regarding the number of those affected by the disease in this study.

Identifying and expanding the role of movement and travel on the dynamics of pandemic influenza may represent another valuable direction for future research. Currently, the agents in MASSAPIS implement just one itinerary out of the following predefined three—family, work/school, and random. But their capabilities can be extended to include other itineraries such as air travel, road travel, and hospital visits that are certainly factors that can influence the spread of infection during an outbreak. Expanding the role of movement and travel to include additional itineraries can greatly enhance the ability get better results from MASSAPIS.

Improving the vaccination scheme from the universal approach currently employed to a targeted scheme which is more realistic may also represent a useful future research focus. Since vaccination is widely regarded as the most effective way to contain the spread, it makes good sense to implement a vaccination scheme targeted at certain individuals considered more vulnerable to the disease in the population, for example, school-age children, the elderly, and health workers [93, 179, 125, 270].

Last but not least, further studies in computational epidemiology are needed to help produce higher resolution models that move us closer towards better model realism. This should be a multi-disciplinary approach that will bring researchers from fields ranging from the social sciences to the health sciences to computing sciences to help design the next generation of models that will better incorporate the dynamics of human behavior into behavior-disease models such as MASSAPIS.

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